CHLAMYDIAL INFECTION IN PREGNANCY: AN ASSOCIATION WITH LOW BIRTH WEIGHT

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

1999

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by

Karla Schmitt

This study is dedicated to my parents John and Ardelle Schmitt. Their life has long been an example of hard work, love and commitment to each other, their children and grand children. They have always provided generous support to the dreams we each have had and more importantly never doubted our ability to achieve them. They will always remain a powerful influence and beacon light for the path ahead, and for each of "my tomorrows."

ACKNOWLEDGMENTS

I would like to thank my committee chair, Dr. Sharleen Simpson, who for the duration of several years and from great distances has been a mentor and provided generous guidance. And each of my committee members, Dr. Charles Mahan, Dr. Donna Treloar, Dr. Lois Malasanos and Dr. James Stansbury, the contribution of their expertise and, most notably, their consistent availability for consultation.

I would like to acknowledge with appreciation the following individuals whose contributions have been significant and without whom this study would not have happened! The relational database was prepared through the assistance and many hours contributed by Alwin Chang, Ken Kampert, Melodee Dew and Karen Freeman. Dan Thompson provided generous time and support to all steps of the statistical analyses. Phil Moncrief provided willing guidance on my intepretation of the case morbidity system and syphilis findings. The patient teaching of many colleagues strengthened the scope of content contained in this work. The extensive assistance of Deberah Keith provided organization to my wandering path on countless occasions. Jack Wroten encouraged my professional growth and achievement through his exemplary leadership, and allowed me the opportunity to explore a topic of enduring interest.

Finally, I would like to thank my family and friends for their loving support words of encouragement, tolerance, nourishing meals and many spontaneous acts of kindness.

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Abstract of Dissertation Presented to the Graduate School
of the University of Florida in Partial Fulfillment of the
Requirements for the Degree of Doctor of Philosophy

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December 1999

Chair: Sharleen H. Simpson
Major Department: College of Nursing

The purpose of this study was to determine whether infection with *Chlamydia trachomatis* during pregnancy was associated with low birth weight. A retrospective population based study was conducted on a sample of 14,002 records. The records were extracted from a large relational database constructed from birth and fetal death records, prenatal risk screening records, sexually transmitted case reports and laboratory test reports. Extensive independent indicator variables were created to control for potential interaction between known risk factors and chlamydial infection. Descriptive, bi-variate and logistic regression analyses were conducted.

Statistically significant associations were observed among women with inadequate weight gain, chlamydia infection and low birth weight at 95% confidence interval (OR 1.98, $p < 0.02$). A stronger association was observed with pre-term low birth weight (OR

2.34, p <0.01). Other risk factors identified as strongly associated with low birth weight in this population were mother reporting a history of prior poor pregnancy outcome, alcohol use, smoking, mother having been low birth weight herself.

Among women who had adequate weight gain, gonorrhea infection increased the likelihood of having a pre-term low birth weight infant by more than five times (OR 5.11, p<0.003). Women of black race and smoking were also significantly associated with low birth weight in this group.

This study indicates that chlamydia infection in pregnancy is strongly associated with low birth weight and that along with other sexually transmitted infections is a significant public health problem that warrants further investigation.

CHAPTER 1
INTRODUCTION

Problem Statement

Chlamydia trachomatis is the most commonly reported sexually transmissible disease in the United States since 1995. The national rates for *Chlamydia trachomatis* are particularly high among women, ranging from fewer than 150 to more than 300 cases per 100,000 female population during recent years (CDC, 1996a, 1997c, 1998a). Among populations of childbearing women, case report rates vary by age, race, socioeconomic status, service setting, and area of the country. Young women are most at risk for infection, with national case report rates during 1997 as high as 2,044 per 100,000 among females age 15-19 years and higher in Florida at 2,208 per 100,000 among females age 15-19 years (CDC, 1998a; Florida Department of Health, 1997a).

Trends in prevalence rates for chlamydia are not well established because, while some states have been reporting the disease since the 1980s, others began as recently as 1995. A national survey of 405 facilities indicated that the number of facilities that provided testing for chlamydia increased, from 160 in 1993 to 288 facilities in 1994, the year of the survey (Beck-Sague et al., 1996). In the population from which this study sample was drawn, the estimated prevalence of chlamydia among pregnant women during 1995 was 9.1% in those under 14 years old, 8.8% in women aged 15-19 years, and

5.5% in those aged 20-24 years. The rates were lower among women more than 24 years old (Schmitt, 1996a).

Close to 80% of infected females and more than 65% of infected males are asymptomatic (Gaydos et al., 1998; Quinn et al., 1996; Schmitt, 1996b, 1999). Hence the potential exists for undetected and untreated infections, or inadequately treated chlamydial infections to lead to significant morbidity, with an increased risk of postpartum endometritis, ectopic pregnancy, pelvic inflammatory disease, salpingitis, preventable infertility, chronic pain syndromes, septic disseminated infection, spontaneous abortion, pre-term labor, or even death. In the infected neonate chlamydial infections are associated with pneumonia, otitis media, and conjunctivitis (Batteiger, Fraiz, Newhall, Katz, & Jones, 1989; Brunham, Holmes, & Embree, 1990; CDC, 1998b; Berman et al., 1987; Askienazy-Elbhar, 1996; Genc & Mardh, 1996; Harrison & Alexander, 1990; National Academy of Sciences, 1996; Gencay et al., 1995; Datta et al., 1988). *Chlamydia trachomatis* has also been associated with adult and childhood myocarditis and atherosclerosis (Muhlestein et al., 1996; Grayston, Mordhorst, & Wang, 1981). Pathologic synergism has been identified between chlamydia and cervical dysplasia (Paavonen, Koutsky, & Kiviat, 1990; Yla-Outinen et al., 1990). Chlamydia has also been shown to enhance transmission of human immunodeficiency virus infection by three to four fold (Laga et al., 1993; Plummer et al., 1991).

During the last decade there has been an increased awareness of chlamydial infections and reporting of most identified cases of chlamydia (CDC, 1995, 1996b, 1998b). The epidemiology of *Chlamydia trachomatis* during pregnancy suggests a range of prevalence from less than 6% to over 20%, depending on the age, clinic setting and

area of the country (Allaire, Huddleston, Graves, & Nathan, 1998; Gittens, Nichols, & Apuzzio, 1994). Recent research suggests that the bacteria invade human host cells within minutes, cross the placental barrier to invade amniotic cells, and cause chorioamnionitis (Patton et al., 1998; Thomas, Jones, Sbara, Cetrulo, & Reisner, 1990).

During the period from 1981 to 1997, the rates of low birth weight (LBW) have overall decreased from 8.8% to 7.5% nationally (Ventura, Martin, Curtin, & Mathews, 1999). However, since 1988 there has been a creeping upward trend from 6.9 to 7.5 in 1997, the highest since 1973. During this similar period of time in Florida, there has been an increase from 7.5% in 1980 to 8.1% in 1998 (Office of Vital Statistics, 1996a, 1999). Not the entire upward trend is attributable to increases in multiple births among older women secondary to treatment for infertility. Multiple contributing factors have been identified. Nationally, low birth weight among singleton births rose from 6.03% in 1996 to 6.08% in 1997, or 4% since 1986 (Ventura, Martin, Curtin, & Mathews, 1999). The group most affected were black women with an increase of 10.3%. Recent analyses of Duval County, Florida births suggest the following factors may be involved with the changing rates: 1) increased numbers of multiple deliveries, by 0.36 for 1998 over the prior year; 2) increased LBW among multiple births, especially twins; 3) LBW among singleton deliveries has increased; 4) increased numbers of births to women of black race/ethnicity, up 3% in 1998; and 5) a downward trend for births reported with macrosomia (Gest, Thompson, & Hopkins, 1999).

Nationally the numbers of women who initiated prenatal care early and received at least the recommended number of visits increased during the period from 1981 to 1995 (Kogan et al., 1998). Yet the rates of low birth weight have continued to rise slowly. One

possible factor may be the understudied role of sexually transmitted infections in adverse pregnancy outcomes. A recent study estimates that 4.8% of LBW is attributable to infection with *Chlamydia trachomatis* during pregnancy in populations with positive test results comparable to that observed in statewide samples (Mittendorf et al., 1994).

Purpose of the Study

This investigator and colleagues conducted a prior pilot study with 2,885 birth records and *Chlamydia trachomatis* test results during 1997. The findings from this Florida study found LBW rates were slightly lower in the sample population than in the statewide population. Among the women with positive test results for chlamydia during pregnancy, the LBW rate exceeded that of women with negative test results. Adjusted LBW odds ratios for chlamydia, smoking, and black race were significant at the 95% confidence level. Odds ratios were 2.17, 2.49, and 2.09 respectively. The adjusted odds ratios of chlamydia and smoking were highest for term LBW, 2.68 and 2.93, respectively. Therefore this larger study was designed to further examine potential associations between *Chlamydia trachomatis* and birth outcomes among a population-based sample of pregnant women and adolescents who initiated prenatal care through county health departments.

Research Question

The following research question was asked in this dissertation: What association(s) exist(s) between low birth weight and *Chlamydia trachomatis* infection during pregnancy?

Definition of Terms

The following definitions were used in this study.

Asymptomatic refers to an absence of symptoms e.g., discharge from urethra or vagina, vulvar itching, intermittent pelvic pain, change in menstrual flow or consistency, burning on urination, or vaginal discharge with an odor. Symptoms are different from signs that the clinician identifies as indicative of the presence of infectious processes e.g., "frothy green discharge versus adherent white clumping discharge," painless ulcer visualized on the surface of the cervix, or palpable mass on the ovary. At times symptoms may be present but the individual may not recognize them as such due to their frequency of occurrence, or unawareness of their relevance in regard to their health, e.g., inter-menstrual spotting.

Chlamydia is the common term used to refer to *Chlamydia trachomatis*. It is the most common sexually transmitted infection in the United States, capable of causing long-term adverse and permanent sequelae.

Chlamydia trachomatis is an obligate intracellular parasite that requires a host cell in order to live and reproduce. In the context of this study those serovars that cause genital and congenital infections are the reference. Several other serovars are the cause of lymphogranuloma venereum or "LGV."

DNA hybridization is a laboratory technique used to increase the likelihood of detecting genetic material specific to chlamydia and gonorrhea present in the test specimen. This technique is used for Gen-Probe PACE2® testing and was employed by the laboratories participating in this study.

EIA, enzyme immunoassay, is one of the earlier non-culture tests for chlamydia. This method detects chlamydial antigens measured by enzyme-linked immunoassay with polyclonal or monoclonal antibodies.

Fetal growth restriction or retardation is defined as a birth weight and height below the 10th percentile for a specific gestational age. Another term that is often used interchangeably is "small for gestational age."

Gonorrhea is the common term used to refer to *Neisseria gonorrhoeae*, a gram-negative intracellular diplococcus, predominantly sexually transmitted, and capable of causing long-term adverse sequelae when untreated.

Inadequate specimen indicates a Gen-Probe test specimen that does not contain enough cellular material to test for the presence of *Chlamydia trachomatis* or *Neisseria gonorrhoeae.*

Indeterminate is a term used to report specimens that do not fall distinctly within the parameters used to measure relative light units on Gen-Probe testing equipment. This may indicate a specimen that is a false negative, a false positive, or a specimen that had inadequate quantity on which to complete the confirmatory test.

Late syphilis is a term used to refer to the period of syphilis infection that continues after the cessation of clinical manifestations and symptoms, associated with primary and secondary syphilis infection. The organism, *T. Pallidum,* is still present, primarily in the spleen and lymph nodes. Early latent syphilis spans the period of the first year of infection. Late latent begins one year after infection, and may last a life time. As during primary and secondary syphilis, a pregnant woman with latent syphilis can

transmit the infection to the fetus in utero. Tertiary syphilis may occur at any time during latency and congenital transmission at this stage is rare.

LCR is a brand name for ligase chain reaction, which is based on polymerase chain reaction, a DNA amplification technology.

Low birth weight (LBW) is the term used to indicate a live born infant whose weight is less than 2,500 grams.

Pooling is the term used to indicate a testing methodology where a portion of multiple specimens are combined in a single vial and all are tested simultaneously. If negative, all are reported out as negative. If the pooled result is positive, then each specimen must be further tested individually to identify the positive specimen. In populations with low prevalence, pooling is a cost saving procedure that conserves reagents. It is not useful in populations with high prevalence of infection.

Pre-term low birth weight (PTLBW) is the term used to indicate a live born infant whose weight is less than 2,500 grams and less than 37 weeks gestation.

Sensitivity of a test as used in this study, is the probability of the Gen-Probe test to report a positive test in an individual truly infected with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

Serology is the term used to indicate a laboratory test technique using blood serum for testing. This is also commonly used to indicate a syphilis blood test.

Serovars of *Chlamydia* species appear to be associated with different levels of immune response and virulence in the human host.

Specificity of a test as used in this study is the probability of the Gen-Probe test to report a negative test in an individual truly not infected with *Chlamydia trachomatis* or *Neisseria gonorrhoeae*.

STD or STI refers to sexually transmitted diseases or infections. In the past this group of infections was known as "venereal diseases." These are the "commonly" known STDs and other STDs less well known to clinicians and the public as sexually transmittable. The commonly known STDs include syphilis, gonorrhea, trichomonas, chlamydia, and HIV. Cytomegalovirus, hepatitis B and C, group B *Streptococcus,* and bacterial vaginosis are among those infections less well recognized as sexually transmitted. Those infections for which common and reliable testing is available are routinely reported to state health agencies as required by law. For other less frequently reported infections, there are generally no reasonably priced and sensitive tests available for use by clinicians to assist in diagnosis. As a consequence, reporting is dependent upon clinician recognition of syndromes and diagnosis.

Term low birth weight (TLBW) is the term used to indicate a live born infant whose weight is less than 2,500 grams and 37 or more weeks gestation.

Unsatisfactory specimen indicates a Gen-Probe test specimen that contains excessive amount of blood, mucous, or other material that interferes with the testing procedure and is reported as an unsatisfactory specimen.

Very low birth weight (VLBW) is the term used to indicate a live born infant whose weight is less than 1,500 grams and less than 37 weeks gestation.

CHAPTER 2
REVIEW OF THE LITERATURE

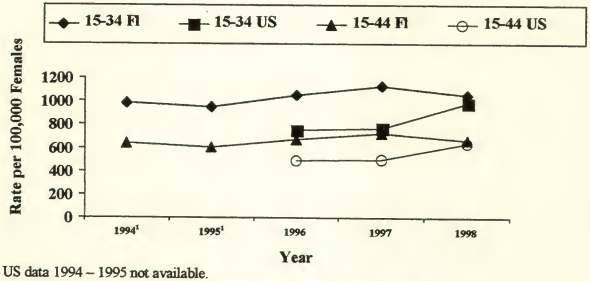
The specific aim of this chapter is to review the literature relevant to the research question. This chapter will consist of eight sections. The epidemiology, biology, and pathogenesis of *Chlamydia trachomatis* will be reviewed. The epidemiology of low birth weight and common risk factors for low birth weight will be covered in other sections. Finally laboratory diagnosis of chlamydial infections, confounding factors related to specimen collection, testing standards for the specific test used in this study, and the sensitivity and specificity of tests available for the detection of *Chlamydia trachomatis* will be discussed.

Epidemiology and Prevalence of *Chlamydia trachomatis*

"Infection in the female reproductive tract (especially in the cervix) can cause premature rupture of membranes and induce premature labor [and] this is responsible for many preventable infant deaths," 1950 quote attributable to I. C. Knox and J. K. Horner (McGregor & French, 1997).

Chlamydia trachomatis has led the list of nationally reportable diseases since 1995. Chlamydia and other sexually transmitted diseases such as gonorrhea, AIDS, primary and secondary syphilis, and hepatitis B accounted for 87% of the top ten most frequently

reported diseases in 1995 (CDC, 1996b). National reporting for chlamydial infections dates to 1995 (with the exception of the state of New York, as only New York City reports, and of Georgia, where only cases diagnosed in women are reportable). The estimated incidence of chlamydia cases is 4 million annually in the United States, mostly among adolescents and young adults (National Academy of Sciences, 1996). In Florida during 1996, *Chlamydia trachomatis* accounted for 52.6% of all sexually transmitted disease case reports, with 81.3% from females and with 78% from women of reproductive



[1] US data 1994 – 1995 not available.
Content from: Florida Department of Health, 1999; CDC, 1998a, 1999a.

Figure 1. Chlamydia Rates per 100,000 Females, aged 15 – 44 Years: Florida and the United States, 1994 – 1998.

age of 15-44 years. The distribution is markedly more notable among the youngest of women with about 44% of cases reported from those between the ages of 15 and 19 years. Figure 1 compares the rate of reported cases per 100,000 female population aged 15-34 years and 15-44 years in Florida to the United States.

Widespread screening activities among different populations and clinic settings have demonstrated rates of infection from 3% to 25%. The positive rates in 1997 among women 15-24 years of age, screened in family planning clinics nationally ranged from less than 4% to greater than 11% (CDC, 1997b). A national population based survey of 1,144 participants aged 12 to 39 years, of whom 54% were female, demonstrated a 10% chlamydial infection from urine specimens (Mertz et al., 1998). The specimens were collected from persons not seeking medical care and contacted in their households as part of the study to estimate the prevalence of various diseases and conditions in a non-institutionalized United States population. Brodine et al. (1998) using ligase chain reaction (LCR) urine technology reported positive rates of 2.7% among female naval personnel assigned to an anchored ship, compared to 6.9% among those living on the naval base located on shore. The average ages for these two groups were 25 and 27 years respectively. Rates drop off significantly in age groups over 24 years, while serologic evidence rises to about 50% of the population by age 30 years (Stamm, 1988)

Screening for chlamydia conducted in adolescents demonstrates the highest positivity in the younger ages. Burstein et al. (1998) reported 24.1 % among adolescents on initial visit and 13.9% on repeat visits. The investigators prospectively examined 3,202 sexually active females, following them for 33 months. Both urine and cervical specimens were tested by PCR. Rates in female military recruits were also high. Gaydos et al. (1998) using urine LCR reported chlamydial infection was 9.2% to 12.2% among 17-year-old recruits, with rates higher for those from five of the southeastern states, Florida not included. Screening conducted using EIA among U.S. Job Corps females aged 16-24 years during 1990-1994, shows 14.5% for Florida applicants (Shakarishvilli, 1995).

Authors reporting on a prospective cohort study among urban adolescents reported initial chlamydial infection rates of 23.2% and 20.8% at follow-up (Oh et al., 1996). The study conducted in the southeastern United States used the tissue-culture method. Specimens collected for culture of *Neisseria gonorrhoeae* were found to be positive for 11.6% of the study group at their initial examination and again for 17.1 % at the follow-up screening 12-24 months later. This is not an uncommon finding to observe dual infection with chlamydia and gonorrhea among a certain proportion of any population studied. From 20-30% of those infected with gonorrhea are co-infected with chlamydia in other studies (Hook & Hansfield, 1999; CDC, 1998b).

In Florida, during the first half of 1999 the rate of positivity for females in family planning, STD, and prenatal clinics participating in the infertility prevention project was 4.45%, 10.82%, and 6.42% respectively. (Baden, 1999). The positivity for different groups of young women tested was 5.44% (15-19) and 3.79% (20-24) for young women in family planning clinics, 12.88% (15-19) and 12.09% (20-24) for young women in STD clinics, and 9.21% (15-19) and 5.21% (20-24) for young women in prenatal clinics. These rates are similar to those observed during 1996 and 1998 among these same populations (Schmitt, 1996b, 1999).

Chlamydia trachomatis is primarily an asymptomatic infection and disease process known to contribute to widespread community transmission among unsuspecting sexual partners. Improved testing technologies in recent years have helped elucidate that the previously believed disparity between asymptomatic infection in males and females does not really exist. Males and females both have very high rates of chlamydial infections. Among female populations screened in Florida as many as 80-85% and among males 70-

75% are asymptomatic when infected (Schmitt, 1999). Nationally, the reported asymptomatic rate ranges from 50-75% (Cates & Wasserheit, 1991). Following exposure and infection, symptoms may begin within 1 to 2 weeks. Females generally present with cervicitis however urethritis is also common. Asymptomatic infection of the rectum or urethra may accompany symptomatic infection of the cervix up to 50% of the time (Cates & Wasserheit, 1991; Stamm, 1999). Many women will have only mild symptoms of vaginal discharge, spotting, lower abdominal pain, or dysuria. Infection may also present as salpingitis, endometritis, peritonitis, Bartholinitis, perihepatitis, pharyngitis, and reactive arthritis. Adults, like infants, can present with conjunctivitis and cases of myocarditis have been reported (Stamm & Holmes, 1990; Freund, 1992; Bergstrom & Libombo, 1995; Berman et al., 1987; Grayston, Mordhorst, & Wang, 1981; Kessler, Pierer, Stuenzner, Auer-Grumbach, Haller, & Marth, 1994).

The natural history of the infection in a nonpregnant woman is one initially of cervicitis, with ascent to cause salpingitis, sometimes having first caused endometritis en route. Without treatment, one-fourth to one-half of women with chlamydia will go on to develop pelvic inflammatory disease (PID), involving inflammation of the endometrium, fallopian tube(s), and potential involvement of the peritoneum. Rates of identification of *Chlamydia trachomatis* by culture, antigen, or serology in cases of salpingitis and PID range from 5 to 55% depending on the clinic setting, geographic site, type technology and country (Cates & Brunham, 1999; Schachter, 1999a). The leading hypothesis for PID pathogenesis is that endometrial and *Chlamydia trachomatis* and *Neisseria gonorrhoeae* initiate tubal infection. Then secondary groups of anaerobic and aerobic bacteria may invade to contribute to the inflammatory disease process (Cates, Rolfs, & Aral, 1990;

Martens, Young, Uribe, Buttram, & Faro, 1993). Reported recovery from women examined by laparoscopy has ranged from 10% to 80%, with secondary bacteria recovered much less frequently. More often in clinically milder or "silent PID," chlamydia is recovered or there is immunologic evidence of recent infection with *Chlamydia trachomatis* (Patton et al., 1994). Tubal scarring and development of tubal infertility follow the acute or silent PID. This same scarring can set the stage for later life threatening ectopic pregnancy events. Moore and Cates (1990) suggest that infertility may follow either acute or clinically detected PID and silent salpingitis. They and others provide ample evidence to suggest that the majority of tubal factor infertility follows events of silent salpingitis, in women who report no history of PID but demonstrate serologic evidence of prior chlamydial infection (Cates & Wasserheit, 1991; Patton et al., 1989; Westrom, 1975, 1994; WHO, 1995). In contrast the Wolner-Hanssen (1995) in-depth study using laproscopy and questionnaires suggests that 'silent' PID is secondary to the failure of the medical community to elicit more complete information from a patient regarding their menstrual history, abdominal pain, and episodes of infection. The author does not suggest that chlamydia is not associated with PID, merely that the silent or atypical status of the PID experienced by women is likely overstated and a result of failure to elicit complete medical histories.

Studies conducted among pregnant women have identified rates of less than 6% to close to 33% infected depending on the age, clinic setting, and area of residence. Allaire and others found a rate of 14.8% among a high-risk indigent obstetric population using both rNA hybridization and enzyme immunoassay (1998). Nearly 21% prevealce was reported by researchers who studied an adolescent pregnant group using immunoassay

(Gittens, Nichols & Apuzzio, 1994). In that same study 25% had more than one sexually transmitted infection. Cohen and colleagues (1990) reported 5.75% prevalence using direct antigen methods. Another group of researchers who cultured vaginal lavage specimens after premature rupture of the membranes found 14% positive for chlamydia (Harger et al., 1991). Nearly 22% prevalence based on culture was reported for initial prenatal visits among urban lower socioeconomic women (Ryan, Abdella, McNeeley, Baselski, & Drummond, 1990). Using two antigen detection systems researchers reported that specimens collected from pregnant women had higher rates of inclusions than those collected from nonpregnant women. However the difference was not statistically significant ($p < 0.096$) in this study conducted with a population whose prevalence was 9.1% among nonpregnant women and 12% among pregnant women (Smith et al., 1987).

The natural history of the infection in a pregnant woman is less well understood. There are inconsistent reports and evidence of disease progression from initial chlamydial infections. Among pregnant women infected with *Chlamydia trachomatis*, fetal loss has rarely been reported, premature delivery is experienced by 10-30%, and perinatal infection by 40-70% (Jones, 1999). There is evidence to support a progression from cervicitis with ascent to cause intrauterine infection. Greater than 11% of infants born to women with cervical infection were found to have antichlamydial antibodies in their cord serum (Fejgin et al., 1997). Harger and colleagues (1991) reported a different finding of no chlamydia positive cultures from amniotic fluid in their study of sub clinical chorioamnionitis among asymptomatic afebrile women in pre-term labor with intact membranes. Among patients with premature rupture of membranes in another study, the presence of chlamydial infection neither increased the incidence of chorioamnionitis nor decreased the latent

period from rupture of membranes to delivery (Ismail, Pridjian, Hibbard, Harth, & Moawad, 1992). Chlamydia was identified by amniocentesis from a case of induced labor secondary to suspected chorioamnionitis (Thomas, Jones, Sbarra, Cetrulo, & Reisner, 1990). The cervical specimen was culture positive for *Chlamydia trachomatis, Candidia albicans, U urealyticum,* and group B streptococci. Chlamydial elementary bodies were identified by fluorescent stain in both amniotic fluid and placental tissue specimens suggesting that only these organisms ascended from the lower genital tract to cause infection in the amniotic fluid and fetal membranes.

Stillbirth or neonatal death was reported ten times more often among chlamydia positive women in a study matched with controls for age, marital status, socioeconomic conditions, pregnancy order, and race (Martin et al., 1982). This pregnant population had a cervical infection rate of 6.7%. Gencay et al. reported a stillbirth at 36 weeks gestation with chlamydia DNA positive placental tissue and histologic evidence of *Chlamydia trachomatis* (1995). Thorp and colleagues reported a fetal death at 34 weeks with histologically confirmed *Chlamydia trachomatis* pneumonia on autopsy (1989). Fetal loss perhaps may be more accurately estimated from animal models. Mice models suggest 19.2% intrauterine fetal demise among those chlamydia positive (Oshiro, 1994).

Postpartum endometritis will follow approximately one-third of cases of cervical infection during pregnancy with development of symptoms at 48 hours after delivery (Schachter, 1999). As reported by Watts and Brunham (1999), Wager and fellow researchers in 1980 found 22% of pregnant women with cervical infection during pregnancy developed late postpartum endometritis (1999). Paavonen et al. (1985) suggested nonpregnancy related chlamydial endometritis is characterized by plasma cell

infiltration of the endometrium. This raises the possibility "that such infections are associated with failure of implantation or early pregnancy loss due to spontaneous abortion." However, Sozio and Ness (1998) do not support a relationship between acute chlamydial infection and the subsequent development of spontaneous abortion.

Bell and others (1994) examined the perinatal transmission in relationship to mode of delivery. With the use of both culture and serology, they concluded that chlamydia may be transmitted more often than is suggested by other reports. The transmission rate to the infant was 60% among infected women delivering vaginally (75 of 125 infants). Those women who delivered by caesarian section were not significantly less likely to be infected than those delivered by the vaginal route with cephalic presentation, however the numbers studied were small (10 infants delivered by caesarian section). Two of ten infants (20%) delivered by caesarian section were later found to be infected in the conjunctiva or nasopharynx. Cord blood was tested for IgM antibody to *Chlamydia trachomatis* for 26 of the infants included in the study. In all cases the cord serology was negative; a positive IgM which would have indicated prior intrauterine infection.

As with other adverse outcomes of pregnancy, the causal link between known infection with *Chlamydia trachomatis* and LBW has not been conclusively established. Recent studies have shown an increased risk of low birth weight and premature rupture of the membranes linked to recent chlamydial infection while others failed to identify any associations. Gencay et al. (1995) reported that gestational age was longer among IgG and IgM sero-negative infants. They also found less chorioamnionitis and atelectasis and pneumothorax among the sero-negative group. In another study designed to examine the effect of treatment on pregnancy outcome, low birth weight was reported in 19.6% of

those infants with infection who were not treated as compared with 11.0% that were treated (Ryan, Abdella, McNeeley, Baselski, & Drummond, 1990). This finding was highly significant, at 95% CI, $p<0.0001$. Others found an odds ratio of 1.5 for low birth weight associated with chlamydia positivity (Gravett et al., 1986). Harrison et al. (1983) identified the presence of IgM antibodies among infants born with low birth weight in a population with 8% prevalence on culture. Martius et al., (1988) reported an even higher odds ratio of 3.9 for chlamydia positive pregnancies to be associated with premature rupture of membranes or pre-term labor.

Investigators of the Johns Hopkins Study of Cervicitis and Adverse Pregnancy Outcome reported an odds ratio of 2.4 for intrauterine growth retardation in a population with 15.5% positivity (1989). In contrast, Germain and colleagues (1994) found no association when cultures were taken at 23-26 weeks. Cohen, Veille, and Calkins (1990) identified a non-significant reduction in low birth weight and small-for-gestational-age infants among another treated group when compared to non-treated controls. Hardy et al. (1984) only found association for chlamydial infection and low birth weight if co-infected with *Trichomonas vaginalis*. One unique aspect of this study however was the destruction of the chlamydial McCoy culture cells by the protozoa. This aspect may have confounded the findings of a lack of an association between low birth weight and chlamydia infection. In 1991, Much and Yeh observed a significant difference in the incidence of low birth weight between two groups when one was treated with erythromycin, $p \leq 0.05$. Clearly additional data is needed to help clarify the relationship between chlamydial infections during pregnancy and adverse outcomes.

The difficulty even in the existence of either epidemiologic or statistically significant evidence for a relationship between chlamydial infection and adverse pregnancy outcomes is that neither type of study has provided enough information about the sequence of events. Therefore it is difficult to demonstrate a direct cause and effect relationship between chlamydial infections and adverse pregnancy outcomes. Additionally, the variable signs, symptoms, test types, definitions of variables, timing of the specimen collection during the pregnancy, and inclusion or exclusion of specimen collection to test for other STDs reduces the value of prospective cohort studies conducted to explore the associations between *Chlamydia trachomatis* and pregnancy outcomes.

In the United States *Chlamydia trachomatis* is primarily a sexually acquired genital infection. However the infection is also a serious congenitally acquired infection. Risk of any chlamydial infection among infants born to infected women is estimated at 50% to 75%. Between 35% to 50% of infants born to infected mothers will go on to develop conjunctivitis and 8% to 22% will develop pneumonia (Harrison & Alexander, 1990; Crombleholme, 1991). "Initial perinatal infection involves mucous membranes of the eye, oropharynx, urogenital tract, and the rectum" (page 57, CDC, 1998b). The typical course is inclusion conjunctivitis first noted at 5 to 12 days of age. If left untreated conjunctivitis may result in corneal scarring and vascularization. It may also be aysmptomatic and self-limited (Schulz, Schulte, & Berman, 1992).

Among infants born to infected mothers, 20% to 50% will develop conjunctivitis and 10% to 20% will develop pneumonia and chlamydial respiratory disease syndrome, with increased sensitization of the infant to further chlamydial infections (Datta et al., 1988; Schachter et al., 1986). Schachter et al. (1986) reported sub-clinical rectal and

vaginal infections in 14% of infants at risk ,secondary to exposure during birth to maternal infection. Of interest is the variable temporal delay between sites for identification of positive isolates. All conjunctival infections were detected in less than three weeks. Nasopharyngeal infection was detected sporadically during the first three months, often in the later period with pneumonia. Neonatal rectal isolates overall were detected after two months.

Datta and colleagues (1988) suggested that appreciable infant morbidity might be associated with higher rates of chlamydial prevalence in pregnant women. In their cohort study they compared morbidity in chlamydia exposed infants to non-exposed infants. Among the exposed infants, 37% developed opthalmia neonatorum, and 12% pneumonia (with one fatality). The reported rates of sequelae among those neonates exposed to *Chlamydia trachomatis* ranged from 12% to 80% for ocular infection, and pneumonia, as compared to 0% to 60% in the non-exposed group of infants. This study was a sub-sample of a parallel study comparing the efficacy of tetracycline ointment and silver nitrate solution for postnatal ocular prophylaxis, (Laga et al., 1988). Inadequate treatment response was reported to each of the ocular prophylaxis for both conjunctival complications and pneumonia, extending the morbidity effect. Overall, the incidence of opthalmia neonatorum was reduced by 77% with the use of tetracycline ointment and 68% with the use of silver nitrate solution. Pnuemonia remained the major complication among infants with perinatally acquired chlamydia. The occurrence of both chlamydia pneumonia and opthalmia neonatorum was not prevented by ocular prophylaxis (CDC, 1998b).

The epidemiology of opthalmia would suggest that there is a disparate relationship between the prevalence of chlamydia in the community and the recognition of newborn

cases, due to the uncommonly low reporting levels. Authors of one recent survey study found that providers only reported 42% of gonorrhea, 56% of chlamydia and 58% of primary and secondary syphilis diagnoses (Hammett, Kaufman, Faulkner, Hoagin, & Battaglia, 1996). Between the years 1994 and 1997 the total number of reported chlamydia opthalmia cases for the United States ranged from 152 to 262, while for the same period 48 to 1,560 cases of gonorrhea opthalmia were reported (CDC, 1995, 1996b, 1997b, 1998a). These reported cases inversely reflect the level of reported gonorrhea nationally in women of reproductive age.

Additionally, one is reminded of the inefficacy of drugs currently used for ocular prophylaxis of chlamydia opthalmia at the time of delivery (CDC, 1998b). Drugs currently recommended for ocular prophylaxis include 1 percent silver nitrate, 1 percent tetracycline ointment and 0.5 percent erythromycin (Gutman, 1999; Schachter et al., 1986). While efficacy of these drugs is high for prevention of gonoccocal opthalmia, their efficacy for preventing chalmydia opthalmia is unacceptable. In short, there is no "gold standard" at present for efficacious and comprehensive ocular prophylaxis. Hammerschlag (1999) summarizes the numerous studies and concludes that the information is inconclusive. He notes that none of the drugs studied for ocular prophylaxis is reported to be universally efficacious. He ultimately recommends that effective screening and treatment during pregnancy remains the most effective method of control.

Diagnostic and political considerations further complicate the situation. Nearly all cases of opthalmia are diagnosed after discharge from the hospital. Such cases are often sub-acute and diagnosis requires appropriately collected specimens that contain conjunctival cells, not exudate alone, and the use of sensitive and specific tests. Many

clinicians would prefer not to suggest to parent(s) that a newborn infant be tested for a sexually transmitted disease. Accordingly many will empirically treat infants exhibiting suggestive symptoms with antibiotic ointments, without collecting a specimen. Consequently there are no positive test results reported to authorities. No comprehensive review of all causes of neonatal opthalmia and pneumonia has been conducted nationally or in Florida in recent years. In one study conducted in Florida the authors identified a higher association between gonorrheal opthalmia with hospitals using eyrthromycin for ocular prophylaxis (Desenclos, Garrity, Scaggs, & Wroten, 1992).

Infants may also present with pneumonia, following intra-partum exposure to *Chlamydia trachomatis* (Stamm & Holmes, 1990; Freund, 1992). Chlamydial pneumonia is a far more serious disease sequelae in this country than is conjunctivitis. Often infants may continue to have reduced pulmonary capacity well into childhood. This is demonstrated by abnormal pulmonary function tests and obstructive lung disease as identified in the study by Weiss et al., 1986 (as cited in Hammerschlag, 1999). Between 8 to 22% of infants born to infected mothers will develop pneumonia (Harrison & Alexander, 1990; Crombleholme, 1991). Chlamydial pneumonia presents with a repetitive staccato cough accompanied by tachypnea. Hyperinflation and diffuse infiltrates are noted on chest x-ray. Fever and wheezing are uncommon. Reliable diagnosis is a more invasive affair than testing for ocular infection, with tracheal aspirates and tissue culture more sensitive and specific than nasopharygeal specimens for non-culture testing. Effective treatment often requires a second course of the recommended antibiotic therapy, due to only 80% efficacy of the recommended eyrthromycin (CDC, 1998a).

There are less common reports of adult conjunctival infection. Conjunctivitis of adults results from hand-to-eye self inoculation or partner inoculation during sexual contact. Worldwide conjunctival *Chlamydia trachomatis* is primarily an endemic disease, spread person-to-person or through unsanitary conditions. Affecting several hundred million persons the disease process is both hyperendemic and holoendemic resulting in blindness for millions of people. In holoendemic areas young children acquire the infection, primarily from infected individuals or unsanitary conditions, with many infected by two years of age. In these communities the rates of blindness are the highest following a process of chronic follicular keratoconjunctivitis that results in corneal damage and scarring of the eyelid. Many infected persons in hyperendemic areas sustain less permanent damage, however blindness or badly scarred conjunctiva are not uncommon (Schachter, 1999a; Schachter, 1999b). Lymphogranuloma venereum (LGV) is another manifestation of chlamydial infections, caused by serovars L1, L2, L3 and L4 and affecting lymphatic tissues. After a process of inflammation there is formation of abscess, fibrosis, and obstruction of lymphatic pathways and disfigurement.

Only recently, literature has begun to identify cervical cancer as a sexually acquired condition. Primarily these associations are based on studies examining the role of human papilloma virus. A few studies have suggested that *Chlamydia trachomatis* may contribute a more direct effect to the development of cervical dysplasia rather than act only as a synergistic bystander (Paavonen, Koutsky, & Kiviat, 1990; Lindner, Geerling, Nettum, Miller, & Altman; Yla-Outinen, Lehtinen, Romppanen, Luoto, Rantala, & Paavonen, 1990). Recently Paavonen (1999 as cited by Jancin, 1999) reported that *Chlamydia trachomatis* was significantly associated with invasive squamous cell cervical carcinoma.

This association was significant after adjustment and in the presence of IgG antibodies to the serovars G (OR 6.6), D (OR 3.1), I (OR 4.4) and E (OR 2.3).

Other researchers have identified that cervical epithelial changes are significantly associated with several reproductive tract infections. Singh and colleagues (1995) examined a population of women attending a maternal health center in New Delhi, India. A specimen was collected for a Pap smear. Other specimens were collected to screen for chlamydia, gonorrhea, trichomoniasis, bacterial vaginosis, herpes simplex virus, genital warts, HIV, syphilis, and candidiasis. If indicated, the woman also received a colposcopic-directed biopsy for any atypical lesions. After controlling for interaction the adjusted odds ratio for an association with inflammatory epithelial changes and chlamydia was 21.3, 13.5 for human papillomavirus, and 22.6 for bacterial vaginosis. They observed a significant additive effect: two infections increased the magnitude of inflammatory changes by adjusted OR 31.4 and three infections by 72.6 fold. Young age was mildly protective and parity greater than one increased the risk by OR 1.7

Today in an age of fatal STDs like HIV the rate of chlamydial infection in a community is epidemiologically significant. A growing body of research provides evidence that the population attributable risk from chlamydial infections is a predictor of increased HIV transmission rates among young women and their partners (Laga et al., 1993; Plummer et al., 1991). These researchers studied prostitutes prospectively and reported adjusted odds ratios associating chlamydia with HIV-1 sero-conversion ranging from 3.2 - 5.7 with a median of OR 4.5. Laga and colleagues also calculated a population attributable risk in their study population of 22% for increased HIV transmisson in the presence of

cervical chlamydia. This was more than five time the attributable risk from genital ulcer disease in this group.

In summary *Chlamydia trachomatis* is associated with a profound scope of disease manifestation in the reproductive age woman. These processes range from mildly annoying symptoms to life threatening events. When pregnant women are infected with this bacteria the sequelae may range from spontaneous abortion, premature rupture of membranes, pre-term labor to vertical transmission that results in low birth weight, stillbirth, and infantile pulmonary infections that may cause lifelong damage to the infant's respiratory system. The full impact of this sexually transmitted infection remains to be established.

Epidemiology and Prevalence of Low Birth Weight

The Florida Office of Vital Statistics reported the rate of low birth weight was 8.5% in 1970 and dropped to 7.5% in 1980 (Office of Vital Statistics, 1996a). Between the years from 1985 to 1995 the LBW rate hovered between 7.4% and 7.8%. From 1996 there has been a gradual upward shift to 8.1% total LBW for 1998, with an incrementally upward change also for very low birth weight (VLBW) over the same period (Office of Vital Statistics, 1999). The observations about rates in Florida mirror the gradual upward shift in percentage of low birth weight reported nationally. However the national rates for 1998 are not yet available for comparison. Overall the percent of VLBW and total low birth weight is higher in Florida than for the United States over the period of time presented in Table 1 below.

Nationally the percentage of low birth weight for singletons among Hispanic women has changed very little since 1989 at 5.35% to 1997 at 5.43.% The rate among

non-Hispanic black women has declined slightly during this same period from 12.22% to 11.46%. Among white non-Hispanic women, there has been more fluctuation with an overall trend that has been a slightly upward from 4.60% in 1989 to 4.95% in 1997 (Ventura, Martin, Curtin, & Mathews, 1999). The rate of low birth weight among adolescents 15 to 19 years old in Florida during 1996 was 1.9% for very low birth weight and 9.9% for low birth weight. These numbers are comparable to national rates for low birth weight at 9.5%.

Table 1. Comparison of Percent of Low Birth Weight: Florida and the United States, 1988-1998.

	Florida		United States	
	Very Low Birth Weight <1,500 Grams	Low Birth Weight <2,500 Grams	Very Low Birth Weight <1,500 Grams	Low Birth Weight <2,500 Grams
1988	1.4	7.7	1.2	6.9
1989	1.5	7.7	1.3	7.0
1990	1.5	7.4	1.3	7.0
1991	1.4	7.4	1.3	7.1
1992	1.5	7.4	1.3	7.1
1993	1.4	7.5	1.3	7.2
1994	1.5	7.8	1.3	7.3
1995	1.5	7.7	1.4	7.3
1996	1.5	7.9	1.4	7.4
1997	1.5	8.0	1.4	7.5
1998	1.6	8.1	-	-

Content adapted from Office of Vital Statistics, 1996a, 1999; Ventura, Martin, Curtin, & Mathews, 1998.

The societal impact from low birth weight infants is enormous in terms of medical health care costs and other long-term adverse outcomes. The average cost for the first year of a low birth weight infants medical care has been estimated to exceed $28,058 (this

estimate is from the Office of Technology Assessment, an 1988 estimate adjusted for 1998 dollars by Department of Health, Office of Health Planning and Evaluation.) Recent analysis on Florida birth records for 1985 to 1990 suggest a significant association between low birth weight of 1,500 and 2,499 grams and physical impairment (OR 4.35), profoundly mentally handicapped (OR 4.75), educable mentally handicapped (OR 2.62), and academic problems (OR 1.26) (Resnick et al., 1999). Low birth weight infants are at increased risk of neonatal and infant morbidity and mortality; nearly 70% of all infant mortality, nearly one third of all handicapping conditions (Patient Outcomes Research Team, 1998).

Biology of Chlamydia trachomatis

Chlamydia trachomatis is an intriguing pathogenic bacteria with a long history of human contact and a distinctly unique growth cycle. Pathology associated with the bacteria was first described in Egyptian papyri (Schachter, 1999a). Most likely it predates humankind as a species by billions of years. Halberstaedter and Prowazek first stained conjunctival scrapings from orangutans infected with human trachomatous matter and demonstrated the presence of inclusions in 1907. In 1914 Lindner isolated inclusions from the conjunctival of infants, the genital tracts of their mothers, and the urethras of their fathers (Schachter, 1999a). T'ang and associates contributed the first isolation of *Chlamydia trachomatis* from persons infected with LGV during the 1950s (as cited in Schachter, 1999a). In 1959 Jones, Collier and Smith recovered the bacteria from the cervix of a woman whose infant had opthalmia neonatorum (as cited in Schachter, 1999a). Other historical milestones are summarized in Table 2 below.

Table 2. Historical Milestones in the Recognition and Study of *Chlamydia trachomatis*.

B. C.	Egyptian papyri contain description of trachoma.
18th century	John Hunter first described Lymphogranuloma Venereum (LGV).
1907	Halberstaedter and Prowazek stained conjunctival scrapings from orangutans infected with human trachomatous matter and demonstrated the presence of inclusions.
1911	Lindner isolated inclusions from the conjunctival of infants, the genital tracts of their mothers, and the urethras of their fathers.
c. 1930	*Chlamydia trachomatis* isolated from persons diagnosed with LGV by Macchiavello. Isolate unfortunately lost before confirmed by others.
1941	Respiratory infection in infants first reported by Botsztejn.
1950s	*Chlamydia trachomatis* isolated from persons diagnosed with LGV by T'ang and associates and later confirmed by other researchers.
1959	The first isolate of *Chlamydia trachomatis* from the genital tract (non-LGV) by Jones, Collier and Smith. Obtained from the cervix of a woman whose infant had opthalmia neonatorum.
1964	*Chlamydia trachomatis* recovered from male urethras, in association with epidemiologic studies of conjunctivitis.
1965	Gordon and Quan developed the first clinically useful laboratory procedure for diagnosis with a tissue culture isolation technique of intracytoplasmic inclusions that allowed for results in 48-72 hours.
1966	Dunlap and associates demonstrated that up to one third of men with nongonococcal urethritis had carriage of *Chlamydia trachomatis*.
1980s	Affordable and sensitive non-culture tests become widespread.
1990s	Highly sensitive and specific amplified testing available.

Content adapted from Schachter, 1999b; Hammerschlag, 1999; Chernesky, 1999.

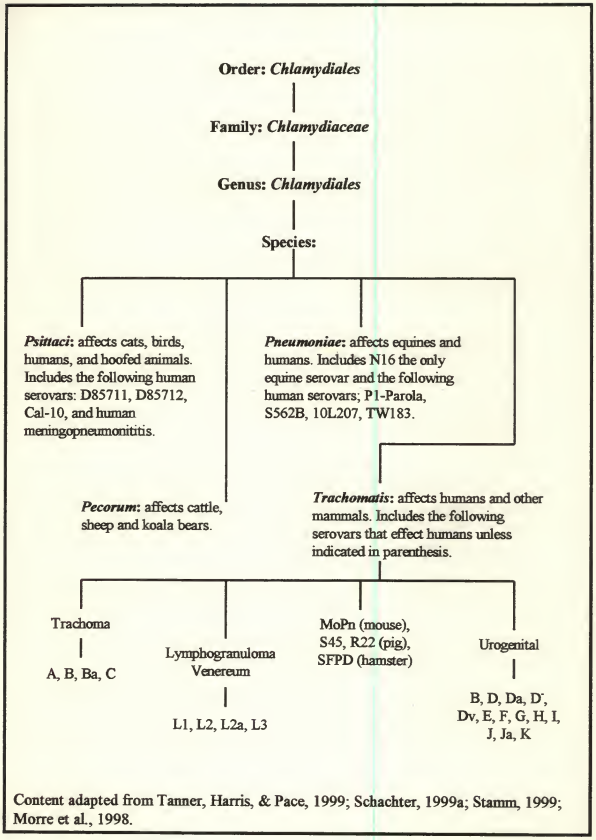


Figure 2. Chlamydiales Tree.

Two of four species in the genus Chlamydia, *Chlamydia trachomatis* and *Chlamydia pneumoniae*, prefer humans as their natural host. Please refer to Figure 2. The other two species are *C. psittaci* and *C. percorum* that prefer birds and lower mammals respectively. However there is cross-over between human, bird and mammalian strains. Twenty-three serovars and perhaps eleven variants for *Chlamydia trachomatis* have been isolated from human specimen by scientists (Schachter, 1999a; Morre et al., 1998; Tanner, Harris, & Pace, 1999; Stamm, 1999).

Developmental Cycle

Due to the unique developmental cycle, chlamydiae merited their own order *Chlamydiales*, and a single family, *Chlamydiaceae*. In their unique growth cycle the bacteria alternate between two morphologic forms. The elementary body (EB) is adapted to the extracellular environment, while the reticulate body (RB) is specialized for intracellular growth processes within the host. The metabolically inactive EB is the infectious form and the RB the metabolically active or replicating form. There are distinct steps in the chlamydiae developmental cycle. The first step is attachment of the elementary body (the infectious particle) to the host cell. Second is entry into the cell. The reticulate particle then undergoes morphologic changes, with intracellular replication and growth. Further morphologic changes of the reticulate particle to elementary bodies, is followed in the final step with release of the infectious particles (Schatcher, 1999a; Schatcher, 1995). The steps are illustrated in Figure 3 below.

Wyrick (1998) provides a concise summary of the current body of information on the cell biology of the chlamydiae gleaned from the scientific community in recent years. The EB

is metabolically inactive and resistant to most environmental challenges, but capable of rapid attachment to the host cell. This attachment is generally held to be aided by some mechanism that triggered adhesion with the assistance of the major outer membrane protein, and generally was held to have occurred within an hour of infection. Newer scientific knowledge suggests adhesion may instead be a parasite-specified phagocytosis, receptor-mediated endocytosis in clarthrin-coated pits, pinocytosis in non-coated pits, chlamydial heat shock protein70 interaction with ATP hydrolysis or movement assisted by host microvilli (Raulston, Davis, Paul, & Wyrick, 1998; Patton, Cummings, Cosgrove, Yvonne & Kuo, 1998; Wentworth, Judson, & Gilchrist, 1991). Most noteworthy is the sheer speed with which the EB can enter the host. Electron microscope observation of the "in vivo" uptake process has recently demonstrated that the EB are assisted by the epithelial cell's microvilli and that internalization is complete within five minutes, and has reached the Golgi apparatus within ten minutes post infection (Patton et al, 1998). This group of researchers suggests that the rapid uptake reflects the bacteria's need to reach the host energy source, as it is incapable of producing energy on its own. Once inside the host cell, a vacuole is formed to envelop the EB, where the EB remain throughout the growth cycle. After a rapid initial fluctuation in pH, a triggered release of tyrosine phosphoylation of the epithelial proteins follows and rearrangement of the chlamydiae's cytoskeleton occurs. There is then an accumulation of F-actin and clathrin which it is believed, aids to redistribute the EB to the peri-nuclear region of the host cell and the resultant highly permeable vacuole formation (Wyrick, 1998; Schatcher, 1999a; Schatcher, 1995). The vacuole becomes what microbiologists term the "chlamydial inclusion body." At this point the chlamydiae "prime" their host for obligate intracellular

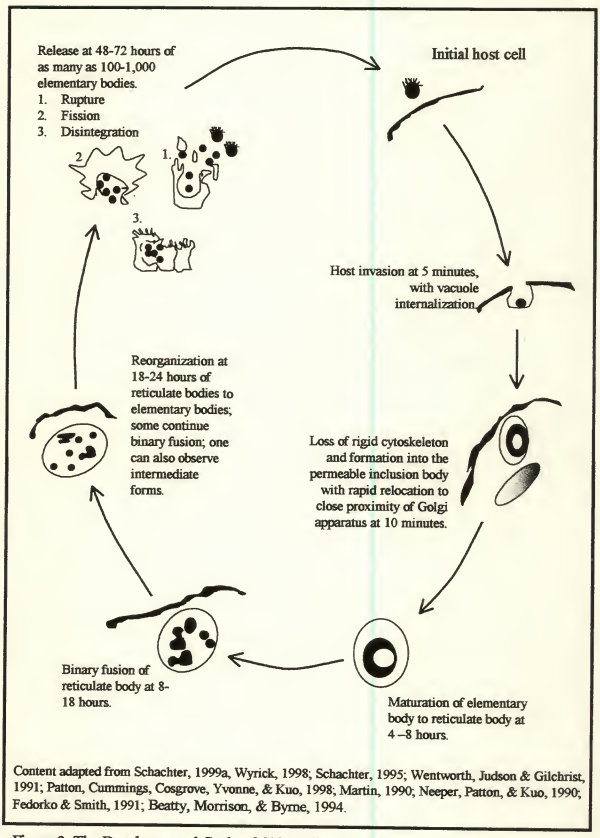


Figure 3. The Developmental Cycle of Chlamydiae.

growth and trigger maturation of the EB into RB. An obligate parasite, chlamydiae utilize the host cell's glycogen, metabolites and ATP in all steps of the developmental cycle. The RB is somewhat larger and richer in RNA than the elementary body. The cycle then progresses to binary fusion of the RB lasting from 20 to 24 hours. During this time another unique activity can be observed: the fusion of multiple inclusions within the host cell to create a single inclusion. After a period of reorganization, triggers that are unclear cause many of the RB to mature into a new group of the smaller EBs in preparation of extracellular exodus. Some RB will continue to divide. At this stage one can also observe intermediate forms (IB) of the bacteria as well (Moulder, J. W., 1974, as cited in Schachter, 1999a). Forty eight to seventy two hours after attachment to the host cell the mature EB is ready for release to infect other epithelial cells. By this time the EBs will occupy the entire cytoplasm of the host cell (Neeper, Patton, & Kuo, 1990). A single inclusion body may release from 100 to more than 1,000 elementary bodies at maturity (Martin, 1990). This release appears to occur in three modes, a volcanic like eruption, fusion with plasma cell membrane, and a gradual disintegration of the cytoplasm, allowing lateral invasion to near by cells. In short, scientists remain challenged by the study of the chlamydiae's developmental cycle with more questions raised than answered in recent years!

When protected by the vacuole, chlamydiae are able to resist the usual hostile onslaughts of the host cell. The intracellular form of *Chlamydia trachomatis* is protected from phagolysosomal fusion, by mechanisms not fully understood. The bacteria is sensitive to iron limitations and shows enhanced uptake of some proteins, e.g., hsp60. The parasite appears able to accept whatever phospholipids available in the host eukayotic cell. The

extracellular form of *Chlamydia trachomatis* is inhibited by penicillins, but is not killed. In this form it is sensitive to temperature, freezing, and dessication. Unlike *C. psittaci* that can live for months in contaminated cat litter, *C. trachomatis* will die at 56°C after 30 minutes. *C. trachomatis* is also sensitive to common household disinfectants (Wyrick, 1998; Schachter, 1995; McCalarty & Hatch, 1998).

Pathophysiology and Pathogenesis

The clinical syndromes associated with *Chlamydia trachomatis* infection are well recognized in the public health community. The pathogenesis of any of the infections attributable to *Chlamydia trachomatis* is not well understood. Of the twenty-three identified serovars, nine are predominant in the genital tract and in infantile pneumonia: D, E, F, G, H, I, J, and K, with D, E, and F found most frequently worldwide. One, B, has been identified in both ocular and genital sites (please refer to Figure 2.). Numerous serovars and variants have only been identified in the last few years (Stephens et al., 1998; Stamm, 1999). Serovars in the C complex grouping (A, C, H, I, J, K) have been identified as more likely to be associated with symptomatic rectal infection among homosexual males (Boisvert, Koutsky, Suchland, & Stamm, 1999). It has been hypothesized that severity of disease may be linked to the serovar. Some studies have supported this; however, serovar F has often been identified in both less asymptomatic or less inflammatory infection as well as in women with upper genital tract infection.

Squamocolumnar epithelial cells are the primary target for non-LGV infections and macrophages for LGV serovars. Initially, focal inflammation with infiltration of polymorphonuclear neutrophils occurs. Mononuclear cell infiltration follows. Abundant

immune response occurs that includes circulating antibodies and cell-mediated responses with both CD-4 and CD-8 T-helper cells. The CD-4 t-cells potentiate the immune response. It appears resolution of the infection is supported by CD-8 cells (Brunham, 1999).

Three models predominate among the numerous models for pathogenesis under consideration (Peeling & Brunham, 1996; Chlamydia Genome Project, 1999). There is a considerable body of work to support consideration of delayed-type hypersensitivity (Beatty, Morrison, & Byrne, 1994; Rank, Sanders, & Patton, 1995 Schachter, 1999a). In this model, re-infection with the same or different serovars leads to inflammation and scarring of the affected mucous membrane. It is possible that the delayed-type hypersensitivity (DTH) model may also result from reactivation of latent infection, possibly triggered by altered levels of steroid hormones. Exogenous progesterone is used in mouse model studies to enhance uptake of chlamydiae, and one study in ewes suggested reactivation of latent chlamydial infection after either estrus or progesterone treatment (Patton & Lichtenwalner, 1998). Others mention that both estrogen and progesterone enhance the growth, survival, and ascent of *Chlamydia trachomatis* in female animal models (Krettek, Arkin, Chaisilwattana & Monif, 1993). While it is unwise to assume findings from animal studies are directly applicable to human pathogenesis of chlamydiae, the role of steroids in DTH merits further investigation.

That latent infection can persist has been a controversial topic among researchers. Some have provided compelling evidence that suggest persistence of a single strain over a period of two to five years (Dean, Suchland, & Stamm, 1998). This group of researchers used serial *omp1* genotyping on recurrent culture-positive specimens and ligase chain

reaction assays on selected intervening culture-negative specimens. In recent years other researchers have used either culture or DNA amplification to examine persistent infection concluding that persistence of infection is not supported (National Chlamydia Committee, 1999a). Hopefully, more conclusive evidence will be forthcoming in the future from researchers.

A suggested alternate model is one of an inflammatory response mediated by human heat-shock proteins and chlamydial heat-shock protein-60 or –70. Chlamydiae evoke persistent host cell production of these pro-inflammatory cytokines. Strong serologic levels of chsp-60 in severe pathology were observed by some groups and reduced serologic response in other groups with milder pathology (Rasmussen et al., 1997; Morrison, Lyng, & Caldwell, 1989; Patton et al., 1994). Witkin and colleagues (1997) suggested that this same model may contribute to the reduced success with in vitro fertilization and embroyo transfer observed among women with high levels of cervical IgA antibodies to *Chlamydia trachomatis*. Other researchers question if the chlamydial heat shock proteins are causally involved in chlamydial immunopathogenesis or merely markers of persistent infection (Peeling & Brunham, 1996).

The third model for pathogenesis of *Chlamydia trachomatis* is one of, genetic susceptibility (Brunham, 1999; Peeling & Brunham, 1996). In this model the data examined supported individual differences in immune responses. Those individuals with weak cell-mediated and strong antibody response were susceptible to re-infection, slower to resolve, and demonstrated more inflammation and disease. In contrast, those individuals with a strong cell-mediated immune response and lower antibody response were less susceptible to both the infection and disease. While the numerous models continue to be

investigated, the actual mechanism of pathogenesis in humans has yet to be proven. There is, however, mounting evidence that the bacteria can and do invade epithelial host cells at different levels of the female reproductive tract, and at different times during the reproductive cycle, e.g., pregnant and non-pregnant states. The role of persistent chlamydial infection is also unclear in the process of pathogenesis. Beatty and colleagues (1994) reviewed the conflicting evidence for persistent infection and concluded that further work following "infected" culture negative persons should be conducted. Byrne (1996) also discussed the work to date on persistence and suggested that certain features associated with in vivo growth of chlamydiae would further support some form of persistent infection. These include the presence of abnormally large intracellular forms of the organism, chlamydial nucleic acid in absence of culturable forms, immunologic evidence of heightened reactivity to stress response proteins, and continuous presence of chlamydial antigen. Bragina, Gomberg and Orlova (1998) reported morphological changes in chlamydial bodies in persons with reported latent chlamydial infection. Others have recently reported in vitro persistence of chlamydial antigens, and chlamydial particles while studying antibiotic efficacy (Dreses-Werringloer, Jurgens, Zeidler, & Kohler, 1998).

Neeper, Patton, and Kuo (1990) provide cinematographic in vitro observation of *Chlamydia trachomatis* growth cycles in primary cultures of human amniotic cells. Of significant note, given the difficulty of culturing this bacterium, were the sustained cycles of infection that occurred, until all amnion epithelial cells in the monolayer had been infected and destroyed. While in this study the amniotic epithelial cells were isolated from the in vivo placental structure, the chlamydiae were capable of damaging the placental

tissues. The study does not conclusively demonstrate how the chlamydiae could actually cross the intact membrane.

Neuer et al. (1996) have suggested that the development of heat shock proteins during mouse embryogenesis is a plausible explanation for differentiated expression of heat shock proteins in early pregnancy using first-trimester decidua and failure of the embryo to implant or survive. Gencay et al. (1996) isolated *Chlamydia trachomatis* from placental tissue. Intra-amniotic chlamydial infection can persist in the absence of clinical symptoms, in the presence of intact membranes, and following apparent eradication of chlamydiae (Askienazy-Elbhar, 1996; Morrison, 1996; Ghaem-Maghami, Hay, & Lewis, 1996; Koehler et al., 1996; Gencay et al., 1997; Neeper, Patton & Kuo, 1990; Brunham, Holmes, & Embree, 1990; Cunningham, 1995).

Laboratory Diagnosis of Chlamydial Infections

According to Lennette (1995) there are three approaches to laboratory diagnosis of infections: 1) direct detection of the organism, 2) cultivation of the organism in a suitable host and 3) use of serology to obtain evidence of recent infection. Direct microscopic examination of the live organism that causes the infection, direct fluorescent antibody technique, and detection of nucleic acids through hybridization or amplification are acceptable technologies for direct detection of the organism. An example of microscopic examination for a sexually transmitted disease pathogen is darkfield microscopy of freshly collected specimens from moist or dry lesions and lymph nodes for *Treponema pallidum* subspecies *pallidum* or Direct Fluorecent Antibody (DFA-TP) technique for body fluids or lesion exudate (Larson, Hunter, & McGrew, 1991). Other

direct visualization examples include gram stain for *Neisseria gonorrhoeae* and saline or potassium hydroxide microscopy for bacteria vaginosis and candidiasis (Lowe & Saxe, 1999). Many commercial enzyme immunoassay tests for chlamydial and gonorrheal antigens, and direct fluorescent antibody for visualization of chlamydial elementary bodies have been available since the 1980s for wide spread screening programs. (Chernesky, 1999; Ehret & Judson, 1991; Fedorko & Smith, 1991). These tests have a sensitivity of 50% to 75% and specificity of 95% to 100% (Pate, Dixon, Hardy, Crosby, & Hook, 1998).

Highly sensitive nucleic acid amplification technology has become available more recently. This method utilizes either target amplification, probe-amplification, or signal amplification to detect minute numbers of organisms in a specimen. These tests are vastly superior overall to culture or any other technology now available with sensitivity ranges of 95% to 100% and 99% to 100% specificity, (Kacena et al., 1998; Everett, Hornnung, & Anderson, 1999; Quinn et al., 1996b). Two other studies with LCR show a similar range of sensitivity. One conducted in France including women of both high (STD clinic) and low risk (prenatal clinic) for chlamydial infection found an overal sensitivity of 95.2% and specificity of 99.6% (de Barbeyrac, Rodriquez, Dutilh, le Roux, & Bebear, 1995). The second study conducted in Florida among subjects from obstetric and gynecological clinics reported the sensitivity as 97.6% and the specificity of 100% (Davis, Riley, Peters, & Rand, 1998).

Pooling of chlamydia specimens will reduce the sensitivity slightly from 100% to 98.4%, but not for gonorrhea specimens as reported by researchers (Kacena et al.,1999; Kacena, Quinn, Hartman, Quinn, & Gaydos, 1999). Pooling can provide even with minor

decreases in sensitivity a significant cost savings of 37% to 46% with pooled sensitivity of 92.8% in pools of four urines and 97.9% in pools of 8 urines (Krepel et al., 1999). Gaydos and colleagues (1998) reported lower sensitivity (88.6%) using amplified testing on urine specimens. Unfortunately, amplified tests remain much more costly than other direct detection methods. Direct detection offers the advantage of rapid results when compared to cultivation in culture mediums. Other advantages are generally affordable cost and high volume capabilities, important considerations for any public health screening program. The disadvantage of the direct detection approach is variable sensitivity and specificity between testing technologies and manufactured products, as well as variable sensitivity and specificity among groups with different prevalence, a phenomenon common to all screening tests.

Cultivation of the organism in a suitable host is the standard by which all other detection methods are compared, especially for medical-legal documentation. This is true for *Chlamydia trachomatis*, even though cell culture is reported to range from 50% to 90% sensitive (Fedorko & Smith, 1991; Newhall et al., 1999). The range of sensitivity is a function of prevalence in the population, laboratory expertise, quality of specimen collection and most often, of specimen transportation. Specimens collected to identify *Chlamydia trachomatis* must be inoculated onto cycloheximide-treated McCoy cells. The specimens should be refrigerated and processed within 48 hours of collection; if the interval will be longer then the specimens should be frozen at – 60° C (Schachter, 1995). These parameters and the bacteria's sensitivity to heat exposure often adversely effect the viability of organisms for cell culture during the transportation interval. These factors

combined with the cost of culture, have contributed to the widespread popularity of the direct detection methods commercially available since the 1980's.

Numerous forms of serologic tests have been useful for the detection of sexually transmitted infections. However, only *T. pallidum*, *C. trachomatis*, human immunodeficiency virus (HIV), hepatitis B virus (HBV), and herpes simplex virus (HSV) have an adequate immune response in current infection for serologic testing (Chernesky, 1999; Chernesky et al., 1998). With these responses there is also significant variability, reducing the reliability of this technique for laboratory diagnosis and restricting its application to specific situations. In the case of *Chlamydia trachomatis* the antibody response elicited during infection may be long lived, therefore serology for identification of lower tract syndromes has not been successful. (Black, 1997, 1998). Serology is useful in diagnosis of infant chlamydial pneumonia and HIV, HBV, and HSV. Serology has been invaluable in the epidemiologic study of chlamydial infections in different populations (Numazaki, 1998; Gencay et al., 1995; Harrison et al., 1983; Numazaki & Chiba, 1996; Numazaki, Kusaka, & Chiba, 1996; Fejgin et al., 1997; Cohen, Tenenbaum, Michaeli, Beyth, & Sarov, 1990). First used as a screening test in diagnosis of non-lesion syphilis before World War II, serology has proven to be very effective in the control of this STD (Brandt, 1985; Pynchon, 1964). However, even with positive serology for *T. pallidum* in an individual for whom a darkfield examination or direct antibody test is not available, confirmation should be sought with the use of a treponemal test technique to identify false positives (Chernesky, 1999; CDC, 1998b).

In populations with low to moderate prevalence, as observed in the study sample, the sensitivity of the non-culture tests range from 50% to 96% and the specificity from 93

to 99% (Dinh & Martens, 1993; Stamm, 1999; Newhall et al., 1999). The direct detection, non-culture test employed to diagnose *Chlamydia trachomatis* genital infections, Gen-Probe PACE2C®, was used in this study. The test manufacturer's published chlamydia sensitivity ranges from 92.5% among those with a high (17.8%) positivity rate to 94.3% among those with a low (4.1%) positivity rate (Gen-Probe Incorporated, 1994a).

Early studies conducted on persons who sought care in Florida county health departments and elsewhere report a sensitivity of 96.4% for the Gen-Probe PACE2C® combination assay among asymptomatic and symptomatic females and males. The prevalence ranged from 6.6% to 9.3% for chlamydia and from 6.6% to 56.5% for gonorrhea, with a combined specificity in this same group of 98.0% (Hale, Melton, Pawlowicz, Halstead & Wright, 1995; Hale, Melton, Lewis, & Willis, 1993; Schwebke & Zajackowski, 1996). This technology may be less sensitive with male urethral specimens. Kluytmans et al. (1991) reported a sensitivity of 70% among a male population with a culture prevalence of 13.2%. In this same group the female sensitivity was 92.7% and prevalence 8.6%.

More recent studies conducted with Gen-Probe PACE2C® compared with DNA amplification tests and other non-culture tests suggest that earlier studies may have over estimated the sensitivity of this nucleic acid hybridization test (Newhall et al., 1999; Wylie, 1998). Wylie et al.(1998) reported a prevalence of 10.4% and sensitivity of 79.3% among a population of females residing in Manitoba Canada. Newhall et al. (1999) found a prevalence of 3.9% and sensitivity of 75.3% and 75.3% respectively, among populations of family planning patients from Washington and Oregon.

Gen-Probe PACE2C® employs the principle of nucleic acid hybridization method. The concept behind this technology is based on the re-pairing of specific nucleotide bases that compose the ribonucleic acid (Foorghani & Erdman, 1995). The double-stranded target ribosomal ribonucleic acid (rRNA) of the chlamydia or gonorrhea organisms is dissociated and re-paired with a chemiluminescent single strand probe which can be read by the testing equipment. This process is based on a biological *in vivo* amplification of rRNA. Many more copies of rRNA (5,000 to 10,000) exist in an individual cell as compared to a single deoxynucleic acid (DNA) strand. This is a different testing methodology from DNA amplification utilized in PCR, LCR, TMA, and SDA testing. As with DNA amplification, rRNA hybridization increases the likelihood that the chlamydia or gonorrhea organisms will be identified in the specimen as compared to some other technologies, however the sensitivity does not approach that of amplification.

Confounding Factors and Quality of STD Specimens Submitted for Testing.

Specimens submitted for chlamydia, or other STD testing, may be adversely affected by any number of clinician-controlled behaviors, laboratory management, transportation interval, and patient-related issues. Among the many variables controlled by the level of clinician skills and knowledge are: choice of collection implements, the presence of excessive blood, mucous, pus or exudate, exfoliated cells, vaginal secretions, debris, fibers, and lubricants included with the specimen(s).

Other factors confounding specimen quality are the availability of supplies in the clinic, types of instruments and implements as well as their consistent supply. This issue is one faced by all providers, public health as well as private (Pachciarz et al., 1992; Steiner,

1989). For example, unavailability of 'large drum' swabs reduce the ease with which a clinician can adequately and efficiently clean the cervix of excess exudate or blood. In one study the use of the cytobrush to collect chlamydial specimens improved the rate of adequate endocervical specimens but not the sensitivity of the enzyme-linked immunosorbent assay used (Kellog, Seiple, Klinedinst, & Levisky, 1992). In contrast, Moncada and colleagues (1989) observed improved sensitivity for both direct flourescent-antibody and enzyme-linked immunosorbent assays with use of the cytobrush. Another group of researchers who compared swab type and storage temperature reported that calcium alginate swabs were toxic to *Chlamydia trachomatis* and herpes simplex virus and that cotton on wood appeared to be inhibitory to chlamydiae (Mahony & Chernesky, 1985). The authors also cite others who reported that wooden shafts were toxic to *Ureaplasma urealyticum* and *Neisseria gonorrhoeae* (Mardh & Zeberg, 1981 as cited in Mahony & Chernesky, 1985). Their concluding recommendation was to use cotton, rayon or dacron tips on aluminum or plastic shafts to increase the viability of specimens for culture.

Training and skills of those sampling the cervix is variable and may affect the quality of the specimen collected. The timing and force with which a swab is rotated within the cervical os may dictate the likelihood of retrieval of adequate numbers of columnar cells, and adversely impact on a positive finding for direct detection tests with lower sensitivity. Because Chlamydiae are obligate intracellular parasites, one must collect the appropriate host cells, columnar epithelial cells located in the cervical os, or at the transition zone. Additionally, the clinician needs to apply adequate pressure and vigorous swabbing to obtain the infected cells (Schachter, 1990).

Contact of the specimen collection swab with the vaginal mucosa on exit from the vagina may introduce confounding inhibitors that interfere with testing equipment and create false readings with DNA amplified technologies. Other inhibitors associated with reduced sensitivity in DNA amplification testing include excessive cervical mucous, talc from latex gloves, and residual urine remaining after DNA purification (National Chlamydia Committee, 1999b).

Patient related variables such as age, recent coitus, and topical medications, lubricants, or spermicides are also potential confounding factors that may adversely affect the quality of the specimen submitted for testing (Bauman, 1993; U.S. Department of Health and Human Services, 1989).

After collection, the actual management of the specimen can adversely affect the quality and the findings. If the recommended temperature is not maintained while in storage prior to transport or during transport the specimen can deteriorate significantly. For example, failure to maintain chlamydial specimens for culture under refrigeration or freezing will reduce viability of the bacteria and the likelihood of a positive culture result and failure to incubate gonorrhea culture specimens at the correct temperature and period of time will reduce their vigor. Submission of small amounts of blood with specimens does not interfere with hybridization test performance; however, grossly bloody specimens may interfere with assay performance (Gen-Probe Incorporated, 1994a). Vaginal secretions and excessive mucopus have been found to interfere with different screening tests and assay performance, including Gen-Probe (Celum et al., 1994).

Standards on Gen-Probe PACE2C® Testing Techniques Within Florida

Testing standards in the Office of Laboratory Services require that all female specimens are first screened with the PACE2C® System, a combination chlamydial and gonococcal nucleic acid hybridization technique. The combination assay allows rapid dual screening for the presence of either *Chlamydia trachomatis* or *Neisseria gonorrhea*. While this first assay does not distinguish between which organisms are present, it is a cost-effective labor reducing approach in populations with lower prevalence, e.g., prenatal clinics compared to STD clinics (Hale, Melton, Pawlowicz, Halstead, & Wright, 1995). All specimens screening positive for the presence of an infection are then re-tested using both the PACE2 Chlamydia and PACE2 Gonorrhea assays. Additionally, all high negative specimens and low positive specimens are re-screened (Farthing, Brumback, Morris, & Wright, 1995). This involves a two step process. The first is a repeat of the PACE2 assay utilizing the chemiluminescent labeled DNA probe specific first for chlamydia, followed by that for gonorrhea. Next the specimen is tested using the Probe Competition Assay (PCA) with reagents that will compete for the target binding sites to form stable DNA-RNA hybrids. A reduction in the signal generated will indicate the specimen contains *Chlamydia trachomatis* or *Neisseria gonorrhea* rRNA contingent on the assay used (Gen-Probe Incorporated, 1994a). The PCA functions as a confirmatory test for questionable results as well as a percentage of all positive findings, an appropriate standard when misdiagnosis of either sexually transmitted infection could lead to psychological anguish or legal ramifications for the patient and/or their partner. Those specimens that originally tested as high negative or low positives but on retesting tested positive or negative respectively, are

reported as "indeterminate" accompanied by the recommendation that the clinician obtain a follow-up specimen for re-testing if the patient has not already been treated for infection.

Test results are calculated based on the difference between the response in relative light units (RLU) recorded from the specimen and the mean of the negative reference readings (Gen-Probe Incorporated, 1994a). Before testing each day, equipment is re-calibrated and cut-off ranges for RLU reading are set.

Related urogenital organisms may be present concomitantly with either chlamydia or gonorrhea. Among these are *Chlamydia psittaci, Ureplasma urealyticum, Gardenella vaginalis,* and *Candida albicans*. Analytical specificity of Gen-Probe indicates these organisms do not cross-react with *Chlamydia trachomatis* or *Neiserria gonorrheae* probes during testing (Gen-Probe Incorporated, 1994b).

Risk Factors for Low Birth Weight

Many variables have been reported in the volumes of literature on risk factors associated with LBW. Investigators have studied the associations between birth outcomes and malnutrition, smoking, reduced or absent social support, employment, violence, work, stress, poverty, age and education, high and chronic stress, low-socioeconomic status, utilization of and access to prenatal care, member of minority ethnic or racial group, drug and alcohol use and infectious diseases. Much of this work has been focused on identification of markers for pre-term birth or low birth weight. Less is known about the role of psychosocial factors and the comparison of these variables for term low birth weight and pre-term outcomes. Some key findings on a number of the potential independent variables are summarized below.

Contribution of psycho-social and behavioral factors. Psychosocial stress was examined prospectively by researchers to identify any associations with LBW in a low-income urban population (Orr, James, Miller, & Barakat, 1996). The researchers used logistic regression with low, moderate, and high stress dichotomous dependent variables controlling for exposure to different stressors. The independent stressors included among others were chronic financial or marital problems, death, divorce, housing, and employment. Scores were not associated with demographic variables such as race, marital status or educational level. For all women, exposure to stressors was closely associated with other clinical and behavioral risks for LBW. There were some different and some similar associations with low birth weight for blacks and whites. Significant for black women were smoking, hypertension, hospitalization during pregnancy, low pre-pregnancy weight, prior pre-term birth, and exposure to stressors. Significant for white women were smoking, drug use, hypertension, hospitalization during pregnancy, and prior pre-term birth.

In contrast, another group of researchers reported finding no association between psychological distress and birth weight for gestational age (Heddegaard, Henrikson, Sabroe, & Secher, 1996). This prospective population-based study collected measures of psychological distress at the 16th and the 30th week of pregnancy by questionnaires among Danish women with singleton pregnancies. Dunkel-Schetter (1998) reviewed numerous studies conducted with colleagues to highlight their findings and possible mechanisms that may contribute to interactive processes between pre-term delivery, anxiety, stress, and stress hormones.

Copper and colleagues (1996) examined stress through measurement of anxiety, self-esteem, mastery, depression, and stress. They reported that stress was associated with PTL, SGA, and LBW after adjustment for maternal behavioral and demographic characteristics. Among black women, this was even more significantly associated. Other researchers identified maternal residence in public housing, poverty, and feelings of helplessness with significant decreases in mean birth weight (Shiono et al., 1997).

The role of maternal employment on LBW and gestation is also conflicting. However two studies conducted with women in other countries suggest that intrauterine growth restriction and PTL may be affected by moderate to heavy physical work effort (Spinillo et al., 1996; Launer, Villar, Kestler, & Onis, 1990).

Smoking during pregnancy has been found to be significantly associated with LBW, TLBW, and PTLBW. Increased risks ranges from OR 2.1 to OR 2.8 and appear to be dose related (Cnattingius & Haglund, 1997; Olsen, 1992; Sexton & Hebel, 1984). One Swedish study examined data for births from 1983 to 1992 and reported a 'true' decrease in smoking during pregnancy and reduction in the attributable risk for SGA infants (Cnattingius & Haglund, 1997). The highest odds ratio, 2.8, was observed each year among women smoking more than ten cigarettes per day.

Another area of study related to smoking and potential LBW is the differences between race and ethnic groups and tobacco use. Among those women who quit smoking sometime during their pregnancy, more women were of white race/ethnicity (12.7%) compared to 4.3% of Hispanic race/ethnicity (Ruggiero & Groot, 1998). Among those women identified as never having smoked the percent was inversely related 41.5% for women of white race/ethnicity and 81.6% of Hispanic race/ethnicity. Ahijevych and

Gillespie (1997) studied nicotine dependence among black and white women and reported differences in plasma cotinine to cigarette ratios. Black women scored higher on plasma cotinine levels; cotinine per cigarette ratio and carbon monoxide boost suggest ethnic differences in nicotine metabolism. They also refer to information from other studies that indicated black women sustained "greater lung damage and less lung function recovery following cessation than their white counterparts." These potential effects of smoking among black women may potentiate the adverse impact on pregnancy and birth weight and merit additional study to better understand the relationship of this risk factor.

Contribution of physiological and medical care factors. Weight gain has been associated with fetal growth and consequent birth weight ranges (Abrams & Laros, 1986; Seidman, Ever-Hadani, & Gale, 1989). Schieve, Cogswell. and Scanlon (1999) examined associations between weight gain per week of pregnancy and net weight gain per week of pregnancy in a low-income urban population. Their findings suggest an association between both low and high weight gain and PTL. They concluded that women with a weekly weight gain at or near the Institute of Medicine guidelines for their respective body mass index had the lowest risk of pre-term delivery. Abrams and Parker (1990) who examined only term pregnancy outcomes reported that a wider range of maternal weight gain than recommended in earlier published guidelines, was associated with good outcomes. They also found no significance between maternal weight gain and SGA infants.

Lumey (1998) examined the effects of under nutrition in pregnancy among infants born during 1944-1946 in the Netherlands and hypothesized that potential biological compensatory mechanisms increase placental growth in conditions of under nutrition. The

placental weight was compared to birth weight, and the average national maternal food ration during the war years was used to estimate under nutrition. Among infants exposed to the risk factor in the third trimester, mean birthweight decreased. No change in birth weight was observed among infants exposed in the first trimester, but there was an increase in placental weight and index to the birth weight. The author also references other studies that have reported an increase in placental index in the presence of anemia and maternal smoking. Another study that examined Women Infant and Children (WIC) program enrollment identified a small but significant protective odds ratio for small for gestational age the longer that a women was enrolled in the program (Ahluwalia, Hogan, Grummer-Strawn, Colville, & Peterson, 1998).

Hickey, Cliver, Goldenberg, McNeal, and Hoffman (1997) examined risk factors that might contribute to low prenatal weight gain. They studied non-obese low-income women and controlled for socio-demographic lifestyle and reproductive characteristics. Three characteristics were associated with significant odds of low prenatal weight gain among women of black race: a mistimed or unwanted pregnancy (OR 2.0), more than one preschool child at home (OR 2.0), and not using her own car for errands (OR 2.1). Among women of white race only, working more than 40 hours per week was associated with low prenatal weight gain (OR 9.1).

Many different measures have appeared in the literature to define and assess the adequacy of prenatal care. Adequacy of care or utilization is then examined along with other variables for its association with LBW. Overall most of these measures recommend initiation into care during the first trimester and then some pre-set number of visits with consideration for length of gestation (Alexander & Kotelchuck, 1996). These measures

overall do not measure content, capture gaps in visits, or adequately consider high-risk pregnancy visit schedules (Stringer, 1998). The inadequacy of the different indices to accurately quantify adequacy is highlighted in the numerous studies that have compared the different measures to the same sample population. Alexander and Kotelchuck applied five measures to data files containing 169,082 singleton births. The proportion of cases assigned to each utilization category (adequate, inadequate, etc.) ranged from 34% to 58% for adequate care, 9% to 20% for inadequate care, and 7% to 27% for intensive utilization.

The Kessner index was applied in a North Carolina study that compared infant birth weight for women receiving their care at the health departments or from other providers who accepted Medicaid (Buescher, Smith, Holliday, & Levine, 1987). Medicaid women who received care from other providers were at twice the risk of having a LBW infant compared to those who received their care at the health department. Augustyn and Maiman (1994) utilized the 1988 Institute of Medicine indices to examine psychological and sociological barriers to prenatal care from the reported literature. Another research group examined the national changing pattern of prenatal care utilization with four of the published indices (Kogan, Martin, Alexander, Kotelchuck, Ventura, & Frigoletto, 1998). Markedly different trends were produced with the different indices. Virtually no change in utilization for adequate or intensive care was reported using the IOM index, while an increasing trend was noted for more adequate and intensive prenatal care utilization was reported with the R-GINDEX and APNCU index. Differing patterns of utilization and trimester of entry for by teenagers ranged from 2.9% to 16.3% and 12.6%respectively.

Marked differences were also noted for utilization with multiple gestations as reported by the different indices ranging from a -13% to 23%.

Perloff and Jaffee (1997) compared two measures to examine the utilization of prenatal care in New York City. The most interesting finding they reported was the marked differences in sample characteristics that the two indices produced. The magnitude of risk for inadequate care among blacks, teens, those women not completing high school, and unmarried women is significantly increased with the use of the APNCUI indices.

Kogan, Alexander, Kotelchuck and Nagey (1994) looked at the content of prenatal care and its association with LBW. They utilized the Kessner Index to measure adequacy of prenatal care utilization and controlled for other risk factors such as age, education, employment status, smoking, etc, and examined interaction terms in their logistic regression models. Women in this study who did not report receiving all types of advice recommended by the Expert Panel on the Content of Prenatal Care were more likely to have a LBW infant (OR 1.38). The authors found no differences between women who reported that they received all the recommended initial prenatal care procedures, and those who reported not to have received all prenatal care procedures. With the discrepancies observed in the above reviews of the different indices the risk associated between LBW and "inadequate care" in this and other studies must be interpreted with caution.

Very young age appears to be associated in some studies with LBW and also late initiation into prenatal care. Higher rates of LBW have also been observed for women over forty. For adolescents aged 15-19 the rate of LBW in 1997 nationally was 13.6%, and for women over forty, the rate was 10%, while the overall rate was 7.5% (Ventura, Martin, Curtin, & Mathews, 1998). Among all women nationally, the percent that entered

prenatal care in the first trimester was 82.5% while only 68.1% of women aged 15-19 entered care in the first trimester.

Adolescents are two times as likely to deliver a LBW infant than are adults (Ventura, Martin, Curtin, & Mathews, 1998). According to Hellerstedt, Pirie and Alexander (1995) parity of the adolescent may also contribute to this observed difference. They reported a difference in LBW rates between primapara (6.5%) and multipara (7.6%) adolescent mothers in their study of adolescent parity and infant mortality. Roth and colleagues (1998) reviewed the literature on young maternal age and the incidence of LBW infants. They noted that the published studies have examined this association from numerous perspectives. One association is young gynecological age, and possible restricted blood supply to the cervix, that in turn may predispose the young female to infections that contribute to preterm delivery. A second theory put forth is nutritional competition for nutrients between the mother and developing fetus. A third theory suggests that combined psychosocial behaviors and conditions like concealment, and accompanying reduced food intake, delayed entry into prenatal care and poverty are the real risk factors, not age. The authors also cite work done by Geronimus to explore the role of race in adolescent LBW rates and noted that the ratio of black LBW to white LBW for 15-19 year olds was 1.8. Geronimus (as cited in Roth, 1998) theorized that it is a lifetime of exposure to racial stress that contributes to the development of "hypetension, a precipitating factor" in pre-term labor and delivery, resulting in LBW.

Swedish researchers examined the births of younger and older women and reported that birth to young women was a social problem, not associated with LBW. The adolescent rate of LBW at 5.4% was better than the overall for women between the ages

of 35 and 49 whose rates were from 9.6% to 8.9% (Hemminki & Gissler, 1996). Their findings in a different population are consistent with much of the epidemiologic data in this country and suggest that the resulting social stigmata and subsequent increased risk for lifetime poverty are greater risk factors for the adolescent compared to the older women for whom the low birth weight event is a greater risk. Lee and colleagues (1988) examined birth records from Illinois for the years between 1980 and 1984. After controlling for race, education, parity, prenatal care, and marital status they concluded that the adjusted risk for low birth weight at term is lowest among teens and increases with advancing maternal age.

Childbearing at an older age in this country is associated with higher rates of low birth weight. For 1996, 8.1% of births to women aged 35-39 were less than 2,500 grams, 9.5% to women aged 40-44 years, and 14.9% to women 45-49 years of age (Ventura, Martin, Curtin, & Mathews, 1998). The rate for women of black race/ethnicity is even more pronounced at advanced childbearing ages: 16% for women 35-39 years, 18.4% for women aged 40-44, and 18.2% for those 45-49 years. Lee (1988, as cited by Committee on Unintended Pregnancy, 1995) suggests that this association may be linked to biologic aging of maternal tissues and systems, or the accumulative effects of diseases e.g., hypertension, diabetes.

The epidemiology of LBW and the literature suggests that black race/ethnicity is disparately associated with LBW, as well as PTLBW and PROM. Virji and Cottington (1991) observed that black women experienced a significant risk for PTL, (adjusted OR 1.56). Others reported an odds ratio of 2.1 for PTL among both black and Hispanic women (Berkowitz, Blackmore-Prince, Lapinski, & Savitz, 1998). Collins and David (1990) examined race and the differential effect of income, education, marital status, and

age on LBW. The risk of LBW remained twice that of white women across all age groups, education, or income strata.

Others have reported that black race/ethnicity is not a risk for LBW when the mother is foreign born and in fact is protective when compared with black United States born counterparts. Cabral and colleagues (1990) observed that foreign-born black women were more likely to be older, married, better educated, have better pre-pregnancy weight for height ratios and adequate prenatal care. Their reported adjusted odds ratio for having a low birth weight infant was 0.81; however, the confidence interval included 1.0 negating the association. Others also suggested that there is a protective effect from foreign birth status with an odds ratio of 0.88 and 0.77 among Caribbean and African-born black women, with the confidence intervals all below 1.0 (Fang, Madhavan, & Alderman, 1999).

Collins and David (1993) examined biracial infants to determine the role of black to white disparity in birthweight. When all variables were entered into logistic regression to control for income, education, marital status, etc, the adjusted odds ratio of LBW for biracial infants born to black mothers and white fathers was 1.4 compared to the biracial infants born to white mothers and black fathers. Biracial infants born to black women also had an increased likelihood of prematurity and SGA, OR 1.6 and 1.7 respectively.

Rural residence has been suggested by some as an adverse situation for access into prenatal care and needed services, with subsequent poor outcomes. Researchers in the northwest examined linked birth records and hospital discharge abstracts stratified by insurance source to examine the effects of poor local access on the risk of having a 'non-normal' infant (Nesbitt, Larson, Rosenblatt, & Hart, 1997). They reported women with poor access expereinced an increased risk of delivering a non-normal neonate (LBW,

PTLBW and increased associated costs). They also noted that women with private insurance were more likely to have higher costs and longer stays overall.

In contrast, Larson, Hart and Rosenblatt (1997) found no association with residence in a non-metropolitan area for LBW or VLBW. They did observe an adverse effect for neonatal mortality and post-neonatal mortality. However, on logistic regression non-metropolitan residence was not associated with either LBW or neonatal mortality. Alexy, Nichols, Heverly, and Garzon (1997) reported that rural or urban residence did not predict LBW. They found race, weight gain, number of total prenatal care visits, and adequacy of diet resulted in stronger associations to predict LBW. O' Campo and colleagues (1997) conducted muti-level modeling to examine macro (census tract) and individual risk factors. They noted all individual level risk factors for LBW had a different effect dependent on the neighborhood of residence. They suggested that housing, crime and unemployment modify the relationship of urban or rural residence to LBW.

Researchers examined the inter-pregnancy intervals (IPI) of small for gestational age (SGA) and pre-term births among a North Carolina population of blacks and whites (Shultz, Arndt, Olshan, Martin, & Royce, 1998). Three categories of IPI were created: 0-3 months, 4-12 months, and 13-24 months. Those with IPI of greater than 24 months were excluded, due to the possibility of sub-fecundity and potential increased risk for low birth weight. Race specific logistic models were used and population attributable risks calculated. Evaluation of single month intervals indicated that the odds ratio for SGA infants was elevated for each until 10-12 months, and decreased with increasing IPI. There was no consistent pattern for pre-term birth associations using the single month incremental analysis. Overall they found a moderate association (OR 1.6) between SGA

and IPI of 0-3 months. No significant association was observed for the IPI of 4 to 24 months.

Prior LBW events and prior pre-term deliveries have been reported as significantly associated with an increased risk for subsequent LBW and PTL events. The birth record and the Healthy Start prenatal screen both contain fields to capture information related to prior poor birth outcomes. Hulsey and others (1998) reported a 2.8 times increased risk for a subsequent pregnancy with PTL, following an initial pre-term delivery. The authors calculated a population attributable risk that attributes 22.5% of second pre-term deliveries to having had one previously. Black women experienced an overall greater rate of pre-term deliveries, but if a white woman delivered prematurely on the first pregnancy she was at a 4.5 times increased risk compared to black women with 2.5 increased risk.

Another risk for poor outcomes may be the role of the father. One study, reported that among women who changed partners after their first delivery before 34 weeks, a 33% reduction in the risk of a subsequent early pre-term delivery was observed compared with those who did not change partners (Li, 1999). Among women who had initially delivered at gestation over 36 weeks, changing partners increased their risks of a subsequent pre-term by 16%. Among women between 34 and 36 weeks no effect was observed with the changing of partners. The weight of the father may also contribute to increased risk of low birth weight delivery for his partner. Klebanoff and others (1998) studied the offspring of an historic Danish cohort combining data from birth registries, military records and midwifery records. They found a significant association between paternal birth weight and the subsequent birth weight of their offspring, independent of the maternal birth weight. Other researchers have demonstrated an association between a woman's birth weight and

the development of pre-eclampsia during their own pregnancies as teenagers or young adults (Innes, Marshall, Byers, & Calonge, 1999).

Contribution of sexually transmitted infections. Dunkel-Schetter (1998) has suggested the possibility that stress increases risky sexual behavior during pregnancy, with reduced prenatal care utilization for the detection of infection. However, she offers no evidence to support this concept. Other literature reports ample associations between intra and inter-uterine infection, low birth weight, spontaneous pre-term labor/delivery and the more commonly known sexually transmitted infections like gonorrhea, syphilis, herpes, trichomonas, and more recently, chlamydia and human immunodeficiency virus. Less commonly known are other diseases often associated with sexually active women, but whose modes of transmission are even less well understood than the historical STDs. These include group B *Streptococcus*, hepatitis B and C, cytomegalovirus, and the many organisms associated with bacterial vaginosis. The more well known adverse pregnancy events associated with STDs include stillbirth, perinatal death, and mental retardation, attributable to early syphilis, herpes, cystomegalovirus, and group B *Streptococcus*, (Goldenberg, Andrews, Yuan, Mackay, & St, Louis, 1999).

Eschenbach (1998) suggests that any amniotic infection is a fetal infection, and consequently may have a role in causality of pre-term delivery before 28 weeks. Other recent studies with chlamydia that have examined pathogenesis of the fetal, and maternal tissues would support such a hypothesis and deserve more consideration.

Not much research has been conducted to examine the direct association between low birth weight and each sexually transmitted infection while controlling for other confounding variables. Researchers have prospectively evaluated the role of *Trichomonas*

vaginalis in low birth weight in a large multi-center study among an ethnically diverse population (Cotch et al., 1991, 1997). They reported at a 95% confidence interval that pregnant women infected with the protozoan were significantly more likely to deliver a low birth weight infant, and to have a pre-term birth weight infant (OR 1.3, and 1.4, $p \leq .01$). Also, infection with *Trichomonas vaginalis* accounted for a disproportionate share of low birth weight deliveries among blacks as compared to whites or Hispanics in this study. Earlier studies found no association between the pathogen and low birth weight (Mason & Brown, 1980; Ross & Middlekoop, 1983, as cited in Wolner-Hanssen, 1999). *Trichomonas vaginalis* is more likely to be found in the squamous epithelium, but evidence has been reported of infection in desquamated cells from human amniotic membranes (Wolner-Hanssen, 1999).

Syphilis was the earliest recognized maternal sexually transmitted infection to be associated with adverse outcomes. One study published in 1917 and another in 1951 identified a transmission rate during pregnancy of 60% to 70% (Schultz, Schulte, & Berman, 1992). While sexual transmission is believed to cease after four years of infection, the possibility of transmission of the spirochete to the fetus by blood-borne transplacental infection is more enduring as demonstrated with a 25% risk of fetal infection during early and 12% during late syphilis (Ingraham, 1951, as cited in Radolf, Sanchez, Schulz, & Murphy, 1999). Many studies have identified the strong association between stillbirth and spontaneous abortion,the most common sequelae, that occurs most often in the 2nd and early 3rd trimesters (Radolf, Sanchez, Schulz, & Murphy, 1999). No literature is available that suggest an association between syphilis and low birth weight while controlling for other confounding variables.

Herpes simplex virus is not associated with low birth weight, and generally is believed to be transmitted intra-partum (Stagno & Whitley, 1999). It is associated with pre-term labor and spontaneous abortion and both primary and recurrent infection can cause fetal infection in utero. The sequelae that can accompany infection range from skin vesicles, blindness, disseminated infection, and long term neurological impairment and most often are lethal. The authors of the NIAID Collaborative Antiviral Study (as cited in Stagno & Whitley, 1999) reported in their data that 33% of those with disseminated infection, 23% of those with central nervous system infection, and 24% of those with skin, eye or mouth infection were delivered before 36 weeks.

Intra pregnancy infection with *Neisseria gonorrhoeae* has been studied by several groups as reported in Gutman (1999) and Morse and Beck-Saque (1999). The rates for premature delivery were between 13% and 67%; however, no mention is made in Gutman of the infants' birth weights or association with term low birth weight, or small for gestational age infants. Other adverse outcomes reported, include spontaneous abortion, perinatal death, perinatal distress, stillbirth, chorioamnionitis, premature rupture of the membranes, skin and joint lesions, and meningoencephalitis (Watts & Brunham, 1999). The reported association of gonorrhea with pre-maturity has been conflicting. Amstey (1976, as cited in Gutman, 1999) reported the rates of poor outcomes in his study were the same, regardless of treatment during pregnancy. Amstey's high rates of pre-maturity were not found by Charles et al. (1970 as cited in Watts & Brunham, 1999). One serious sequelae is an association between pregnancy and disseminated gonoccocal infection, a condition that usually requires hospitalization to adequately treat.

Bacterial vaginosis has been identified in a significant number of studies as strongly associated with pre-term low birth weight. The Vaginal Infections and Prematurity Study Group reported an odds ratio of 1.4 for bacteria vaginosis and preterm delivery of a low birth weight infant (Hillier et al., 1995). The Patient Outcomes Research Team (1998) reported that bacterial vaginosis in women of black race/ethnicity accounts for 40% of excess pre-term births. They also demonstrated that antibiotic treatment for bacterial vaginosis in pregnancy reduced pre-term deliveries. Eschenbach (1999) and Hillier and Holmes (1999) provide comprehensive reviews of bacterial vaginosis. The authors note the strong associations between this infection and adverse pregnancy outcomes, and the positive impact (albeit conflicting impact) that treatment during pregnancy has in reducing incidence of prematurity. Eschenbach also provides a discussion on the potential association between fetal and maternal immune response in the presence of infection with bacterial vaginosis.

The actual impact on low birth weight from bacterial vaginosis is probably underestimated since this condition is roughly twice as common as other reportable STDs and also asymptomatic. However, a recently completed national multi-centered study failed to provide the needed evidence that treatment for bacterial vaginosis during pregnancy reduces the likelihood of prematurity or low birth weight (Hillier, 1998). Two other areas of concern with bacterial vaginosis (BV) are the non-sexual acquisition of the syndrome and the role of BV in HIV acquisition. Black women are three times more likely to have BV regardless of the number of sexual partners, and in the absence of sexual partners. In contrast white women are more likely to develop or acquire the condition with increasing number of partners (Hillier, 1998). Numerous studies suggest that BV enhance

the acquisition of HIV infection during and after pregnancy with adjusted odds ratios of 1.5 to 3.7 (Hillier, 1999).

Nair and others (1993) reported that HIV vertical transmission was increased with the presence of clinical chorioaminionitis, any sexually transmitted infection during pregnancy, and associated with LBW ($p \leq .05$). Those infants born before 35 weeks were significantly smaller than infants non-infected with HIV.

CHAPTER 3
METHODOLOGY

In this chapter the research design, protection of human subjects, confidentiality, data sources, development of the relational database, methodological issues in the use of administrative databases, definition of study variables, data analysis, limitations, and assumptions are addressed.

Research Design

This was a retrospective epidemiological study of a population-based sample of pregnant women and adolescents who initiated prenatal care through county health departments. A relational study database was constructed from linked data files. The files were extracted from numerous administrative databases. The records of infants born during 1996 and their mothers were linked to laboratory tests, disease reports, and prenatal screening information through the use of probabilistic matching algorithms. Descriptive analysis of all files and the extracted study file was conducted. Logistic regression analysis was conducted to further explore the association between infection with *Chlamydia trachomatis* and low birth weight. The data sources, process of matching records, and analysis that was conducted are described in detail below.

Protection of Human Subjects

This was a retrospective epidemiologic analysis of existing data. The University of Florida, Health Center Institutional Review Board, and the Florida Department of Health, Review Council for Human Subjects, both approved the study protocol. The request to waive documentation of informed consent was approved by both groups. No direct contact was made with subjects. No treatment or care was provided or altered for the subjects included in this study. Since this study retrospectively examined existing information, no individual informed consents were deemed necessary by either review body. The reporting of births and fetal deaths and of positive tests diagnostic of the sexually transmitted infections studied and morbidity information is required by law; Chapters 382 and 384, Florida Statutes. The original consents to examine the data sets as outlined in the study protocol were obtained from the respective administrative data managers charged with the confidential maintenance of each data systems that contained the morbidity or vital records. Oversight review for the study was provided by Department of Health Review Council for Human Subjects.

Confidentiality

During the entire duration of the research period, the confidentiality of all data systems was maintained in compliance with confidential security management protocols of the Florida Department of Health. The study data set was stored on a server with access limited to the investigator and four other departmental staff who assisted with the data extraction process. The final study data set constructed through the matching process was password protected and accessible only to the investigator. The researcher was assisted by

departmental staff to extract existing data from multiple data systems maintained for tracking of client clinic services, recording of client laboratory services, and billing. The matching of data files was conducted by departmental staff in the routine course of activities conducted to examine quality of care, evaluate health programs, and manage data systems. All data systems variables were matched with identifiers of the subject intact. All hard copy information and computer files were stored for the duration of the study according to protocol. During analysis, the accumulated data were examined, aggregated, and formatted into a structure useful for analysis without the use of client identifiers.

Data Sources

Variables for the study data set were extracted from six administrative databases. These databases were 1) 1996 birth records; 2) 1996 fetal death records; 3) Healthy Start prenatal screen; 4) Maternal and infant laboratory test results; 5) Maternal and infant case morbidity; and 6) Congenital syphilis records. Each are described below and information is provided about the software, hardware, and flow of the data from point of collection to final repose in the data system from which it was extracted for this study.

Birth and fetal death records. The birth and fetal death records were the first two databases from which study data was extracted. The first statewide vital statistics law for Florida was enacted in 1899, establishing a system for physicians to report births and deaths (Porter, 1901). On January 1, 1917 the first comprehensive registration system based on the national "Model Vital Statistics Act" became effective in Florida, after earlier passage in 1915 by the State Legislature (Fearnside, 1916). The base study file, the birth

record file, is an extraction from this vital statistics database. The fetal death records were also extracted from the vital statistics database. Some of the information regarding birth and death records is similar, and some aspects are dissimilar. The following discussion will note where they are similar and where they are different.

The registration of births and fetal deaths is both a local and state function of 67 local registration districts corresponding to the jurisdictional area of the county health department. (Office of Vital Statistics, 1996b). The county health department director or administrator serves as local registrar for that county. It is his/her responsibility to oversee the timely and complete registration of births and deaths occurring in their district. Once a birth or death event is accepted for registration, the local registrar maintains a copy of the vital record and forwards the original to the state office.

The information contained in the vital birth and death record is obtained from the following sources: mother, father, relatives or persons who have knowledge of the facts, physicians, midwives, funeral directors, and hospital records. A standard form is used to record and register the information required by the vital statistics law, Chapter 382, Florida Statutes. The registration form in use during 1996 reflects the national model birth record (Office of Vital Statistics, 1996b). The Florida birth registration form supports collection of all recommended data from the model birth record, with the notable exception of parental occupation. The hospital administrator (or if the birth is non-institutional, the birth attendant) is required to file within five days after the birth a complete and accurate birth certificate with the local registrar. The certificate must be signed by at least one parent, attesting to the accuracy of the information, and either the hospital administrator or designee, or birth attendant for non-institutional births. Chapter

64V-1 of the Florida Administrative Code provides clear direction on the preparation of the certificate regarding paternity, maternity, birth attendance, the child's name and surname, and residency. Local registrars provide regular training to hospital medical records staff and the clerical staff responsible for completing the birth certificate (Office of Vital Statistics, 1996b; R. Shepard, personal communications, June 30, 1999). The birth record segments reflect the handbook directions and training provided to collect the information from the numerous sources. The first segment has the legal demographic information. This detail should be collected from the mother, father or other person with "knowledge of the facts." The second segment contains the medical and health history information. The medical history detail should be collected from the medical records, with both delivery and prenatal supplied to the hospital (or birth attendant, or center). The details about the condition of the neonate should be collected from the neonatal unit records, e.g., abnormal conditions of the newborn, anesthetic complications, etc.

Clear directions and regularly conducted training sessions do not necessarily translate into accurate completion of birth certificates (Sammet, personal communications, June 30, 1999). During the data entry process at the state registrar's office, a staff member telephones county health departments for clarification if they are unable to decipher data on the birth certificate. Routine quality assurance reports are completed monthly to identify outliers in data field. Habitual problems like late reporting, or high error rates in a particular data fields are generally identified and addressed at the local registrar's level though consultation with the hospital administrators. Persistent problems and unusual outliers in the data are addressed by visits to the hospital from the local registrar or from

state registrar's quality assurance office staff (R. Shepard, personal communications, June 30, 1999).

Florida Statute section 382.002(7) requires that fetal death certificates record "the death of a product of conception prior to the complete expulsion or extraction from its mother, if the twentieth week of gestation has been reached." The statute further provides that every fetal death must be registered within five days after the delivery occurred, and prior burial, disposition, or removal from the state (Office of Vital Statistics, 1996b). The funeral director, direct-disposer, or physician/midwife who attended the delivery and is responsible for registering the record, completes the registration record. The certificate of fetal death is to be signed by the physician in attendance. The midwife may sign as actually having attended the delivery but not as to the cause of death. The hospital administrator is responsible for providing the medical details to the funeral director in charge of the burial/disposition arrangements. The data entry and quality assurance for the fetal death registration is the same as for the birth certificate.

The data entry for both files is conducted on personal computers. The two files are supported by proprietary software and maintained and stored on a mainframe computer system housed in the Department of Children and Families. Hard copies of the data are regularly microfilmed. The two files, the birth record and the fetal death record were extracted in separate programs from their respective databases. Staff in the Department of Heath then combined these two files after realignment of the fields to create one continuous birth fetal death record file. In the routine course of operations at the Office of Vital Statistics these records are maintained separately at all times. Quality assurance measures are regularly employed to assure that infants initially reported as a birth are not

later reported also as a fetal death. Monitoring steps are designed to identify inappropriate registration combinations of certificates for the individual live born infant or stillborn infant. This combined data set provided key variables for the final study database, and are presented in Appendix A. It also served as the base file against which all other files were matched and linked to in the final relational study database.

Healthy Start prenatal screen database. The Healthy Start prenatal screen is the third database from which study files were extracted. In 1991, the Florida Legislature enacted the Healthy Start program with the creation of Chapter 383.2161 of the Florida Statutes and development of Chapter 64C-7, Florida Administrative Code. Implemented in April 1992, this program was modeled on prenatal case management programs in other states like South Carolina and international studies that demonstrated the value of non-medical interventions for women and infants at risk of low birth weight, infant death, and developmental delay (Thompson, 1993; Florida Department of Health, 1997b). The core components of Healthy Start include: 1) universal screening of all pregnant women and newborns, 2) professional assessment of health, social and environmental risks, and 3) targeted case management and risk appropriate care. Expanded Medicaid eligibility to 185% of the federal poverty level, and provider reimbursement to providers to administer the prenatal screens further support the Healthy Start program goals of improved pregnancy outcomes (Florida Department of Health and Rehabilitative Services, 1995). First trimester screens are reimbursed at a higher rate in support of timely intervention (Florida Department of Health, 1998).

The Healthy Start prenatal screen data set was extracted from an existing system database housed in the Florida Department of Health, Office of Vital Statistics,

Jacksonville, Florida. The source document for this data set is the Healthy Start prenatal screen. All prenatal care providers are required by law to administer the screening instrument to pregnant women, preferably at their initial prenatal visit. The screening instrument collects demographic information and responses to a series of "risk" questions. The questions are based on medical, psychosocial, and environmental factors associated with increased risk of poor pregnancy outcomes. A score is calculated based on the risk factor, and the strength of the risk as a predictor of poor outcomes (Serow, Jones, & Luke, 1996). In addition to the demographic, medical and provider information collected, the psychosocial and environmental variables capture risk information about educational level, access to care, housing, and food, drug, alcohol and tobacco use, risk of domestic violence, and perceived level of personal stress.

The particular "risk" factors included were initially based on extensive review of the literature and an evaluation of birth and fetal death records for associations commonly observed in the Florida population among low birth weight infants and infant deaths. Two different years of birth records were evaluated in development of the prenatal screening instrument utilized since 1994. The 1989 birth and fetal death records were used to calculate risk ratios on commonly held risk associations, e.g., age less than 18 years, age over 39 years, unmarried, etc. If a factor occurred in more than 1,000 births and had an associated risk ratio of greater than twice the average risk, then it was considered a potential "risk factor" and included in the initial screening instrument (Thompson, Hopkins, & Watkins, 1993).

After the first two years of use, a second evaluation utilized the prenatal screens and the birth records for the period between April 1, 1992 and April 30, 1993 (Thompson,

Hopkins, & Watkins, 1993). The adverse pregnancy outcomes were birthweight under 2,000 grams and/or birth date of less than 34 weeks from the date of last menses. The same adverse outcomes were used to develop the initial screening instrument after examination of neonatal and postnatal death rates from 1991. It was noted that Florida death rates were high at birth weights below 2,000, and dropped off above this cut-off point as compared to the more universally used 2,500 grams. Likewise the death rates level off above 34 weeks between last menses and birth date. The positive predictive value of each screening tool risk factor was analyzed from the linked birth records and prenatal screens. Additionally, besides effectiveness of the screening tool to identify women at risk of an adverse outcome as defined in the analysis, the related workload to the county health department was considered. At the recommendation of the Healthy Start Advisory Committee, a few subtle changes were subsequently made to the scoring weights and risk factors in the revised 1994 form to achieve a predicted positive screening rate of 39.98% and sensitivity of 60.64%.

One copy of the screening instrument is forwarded to the Office of Vital Statistics for data entry. During 1995 and 1996, the data entry system was constructed to require that all fields were "must enter fields." This data entry system was envisioned as appropriate to aid evaluation of the instrument and the program in the early phase of legislative implementation. Any record that was found to have an incomplete data field was placed in a query status and returned to the local county health department. It was then the responsibility of the local authorities to contact the appropriate public or private prenatal care provider and ensure completion of the missing data (K. Freeman, personal communication, June 30, 1999). During 1997 after the preliminary evaluation, some fields

were changed to reduce the restriction on the data entry process. This change resulted in higher rates of query flags on many variables.

The primary use of the information collected on the prenatal screening instrument is to calculate a risk score and provide the clinician with a platform to seek consent from the woman to assess her need for targeted services. As with other screening instruments, the intent is a rapid reliable assessment of an at-risk status. The data entry process was not envisioned or funded to support a standard consistent with research protocols. During the data entry process verification of the data fields is restricted to four fields: name, social security number, score, and date of the screening event (J. Ballard, personal communication, June 30, 1999). However the Healthy Start coalitions are charged with the responsibility to designate an agency that will provide training to providers on correct use of the form, model successful solicitation of the screening process, and identify patterns of positive risk within the community in order to target resources. Additionally, the county health departments are charged with the responsibility to monitor the screening instruments for completeness and coordinate the collection of missing data on queried forms returned from the Office of Vital Statistics. This data set provided key variables for the final study database, as are presented in Appendix A.

Maternal and infant laboratory test report database. The maternal and infant laboratory test report database is the fourth source from which study files were extracted. The laboratory Gen-Probe PACE2C® test report data set was extracted from an existing system database housed in the Department of Health, Bureau of Laboratories, Jacksonville, Florida. This system was developed to support reporting compliance with state and federal laws and regulations regarding biological specimens submitted for

testing, and timely billing of providers. Following is a review of the system specifications and the flow of data into that system, as regards specimens submitted for testing with the Gen-Probe PACE2C® nucleic acid hybridization technology (S. Crowe, personal communication, June 29, 1999).

Beginning in December 1995, the Florida Department of Health, Bureau of Laboratories commenced implementation of a long-range plan to computerize and store all test-related data in an electronic system. This represented a transfer from a hardcopy filing system based on specimen ascension numbers to an electronic data system, allowing recall of a particular test result(s) from numerous demographic or biological variables, and the ascension number. Additionally, the database was structured to support centralized billing to providers, regardless of the branch laboratory at which the specimen was processed. Each laboratory was brought onto the new system sequentially, beginning with the main branch site that processed the highest volume of specimens. By late-year 1996, all branch laboratory computer systems were functional, as was the central statewide database. During this same period many test reports from the branch laboratories actually were key punched into the system at the central office site, to facilitate the billing process.

The system software written in Massachusetts Utility Multi Programming System (MUMPS) language is a proprietary product. During 1996, it is run on a Unix platform operating system through centralized servers linking the five branch laboratories. Data are entered from personal computers located in each respective area of the laboratory. In the routine course of laboratory operations specimens are received in the delivery/mailroom. At this initial point specimen labeling is matched against test requisition slip data for accuracy, completeness in accordance with state and federal laws, and regulations

regarding biological specimens. A numbering machine is then used to stamp the requisition slips sequentially with coded numbers reflective of the branch laboratory, area of the laboratory in which the test will be conducted, and by specimen ascension. For example "JSGxxxxxxxx" is Jacksonville Serology Gen-Probe followed by the accession number. Preprinted labels are simultaneously numbered with the same accession number by a different machine. These preprinted labels are attached to the specimen vial or container for tracking within the computerized system and through laboratory processing. Specimens then are transported to the respective area of the laboratory to begin testing. On arrival into the respective laboratory areas, laboratory technicians enter the ascension numbers to create the test record in the computer system, along with the date the specimen was received and the name of the test requisitioned. Additionally, the specimens are noted for compliance with acceptable collection to testing time frames according to the individual test type requested. During the period that specimen testing is in progress data entry operators begin to enter the demographic information into the computer record created for each specimen. Variables entered at this stage included: last name, first name, social security number, address, insurance numbers, date of birth, race/ethnicity, sex, date of specimen collection, provider code, program code, county where specimen originated, provider address and name, the patient diagnosis, the physiologic source of the specimen and the laboratory site identifiers.

On completion of the testing process the laboratory technicians check 100% of the demographics on the specimen labels against the data that has been entered into the computer tracking system prior to reporting out the test results on each specimen. This process is aided by a demographic quality assurance report printed out from the system

prior to entry of the test results. During the course of testing the test results are verified and any applicable qualifiers or specimen rejections are entered into the system, along with the names of those reporting the results. Data error can and does occur at the initial phase of specimen and demographic registration into laboratory computer systems. Daily quality assurance activities monitor data entry of demographic information and the reporting of test results.

During 1998, an unfortunate series of events occurred that caused corruption of segments of the database affecting calendar years 1996 and 1997. While much of the primary database was subsequently repaired from archival tapes, not all of 1996 or 1997 test reports could be restored. Hard copy requisition slips are maintained in archival files for the seven-year time period as required for medical records by law, Chapter 483.051(7)(f), Florida Statutes. The extent and the scope of the damage to the electronic operating system and hardware was not identified until many months after this study was conceptualized, the protocols written and approved, and countless hours expended on matching of records to the base study file had commenced. Hence it was impractical at that point to consider re-framing the study around a different birth cohort. Unfortunately, these records are stored according to specimen ascension number. The estimated cost for retrieval of missing test results for subsequent re-entry into the data system would serve no laboratory purpose and was cost prohibitive to this investigator in terms of the study budget. There is no reason to believe that the individual test reports contained in the Gen-Probe test report data set are any more or less complete in any given time segment for the period included in this study. There is reason, however, to believe that the distribution of the test reports is constrained by both the events associated with the implementation of the

computer system and the described corruption event that occurred. The skewed distribution is discussed below in the results chapter. However, one of the strengths of this data set is the representiveness of specimens collected from women receiving prenatal care in county health departments.

In the initial step, an extraction using MUMPS was made from the primary laboratory data system to select data fields with information pertaining to Gen-Probe PACE2C® (S. Shiver, personal communication, June 30, 1999). This extraction was done through the use of programming with Visual Basic to create a database flat file. The files were then transferred onto the Sequel Server subdirectory. (The NT platform operating system replaced the Unix system in late 1998 following the discovery of the system failure.) The files were then accessible through the closed-frame relay departmental wide-area network to the Bureau of STD staff with appropriate authorization and passwords. At the next step FOX PRO programming software was used to construct an ASCI flat file extracting only the desired study variables. In this step some variable fields were made to conform to numeric codes consistent with the base study file, the 1996 Birth Fetal Death Records, (race, ethnicity, county), and the Year 2000 date format (YYYYMMDD). Extraction parameters included: all Gen-Probe PACE2C® reports with collection date between March 1995 through June 1997, for females regardless of date of birth, and reports for males with a date of birth during 1996. The following variables were extracted to support the matching process and for subsequent descriptive analysis: last name, first name, social security number, date of birth, race, sex, address, county, specimen number, date of specimen collection, test type, and results for both *Chlamydia trachomatis* and *Neisseria gonorrheae*. The extraction totaled 214,121 records from the primary laboratory

Gen-Probe PACE2C® database that met the time, test, and gender study parameters. Each woman and infant had two records, one for chlamydia results and a second for gonorrhea results. This data set provided key variables for the final study database, as are presented in Appendix A.

Maternal and infant case morbidity database. The maternal and infant case morbidity database is the fifth source from which study files were extracted. Sporadic reporting of "venereal diseases" by providers to the authorities dates to 1918. By 1920 the numbers of venereal diseases reported exceeded the total of the next three causes of illness (Hardy & Pychon, 1964). In 1921 the Bureau of Venereal Diseases faded into the Bureau of Communicable Diseases and it was not until 1938 that funds were appropriated to support reporting again. Prior to World War II (in 1944) Florida saw the establishment of a central registry for syphilis (Brink, 1944). That same year the Legislature enacted prenatal and premarital serology for syphilis. The present centralized computer dates to 1988 and contains records of 458,771 case reports for syphilis, chlamydia, gonorrhea, chancroid, lymphogranuloma venereum, and since 1997, human immunodeficiency virus (K. Kampert, personal communications, June 30, 1999). The maternal and infant case morbidity data set was extracted from this existing STD Case Morbidity Reporting database housed in the Florida Department of Health, Bureau of STD Prevention and Control, Tallahassee, Florida.

The details of a STD case report travel through numerous hands before actually entering the system, defined as a "case." At the onset a suitable specimen suspicious of a STD must be collected and forwarded to a laboratory for testing. Laws and regulations require that laboratories and physicians both must report all positive tests diagnosing a

reportable sexually transmitted disease per Chapter 384.25, Florida Statutes and Chapter 64D-3, Florida Administrative Code. These reports are made available to the county health department. During 1995 and 1996 the information from positive laboratory reports and physician diagnoses was entered into the morbidity system and then field records were produced to support the activities of disease investigator staff to verify the case details with the physician or other provider. During this same time period, verification of treatment was implemented for gonorrhea and chlamydia. Due to the enormous volume of chlamydia and gonorrhea cases and staffing constraints, this was not previously a requirement. During this time some counties also began to verify the case data, patient treatment, and partner(s) treatment for pregnant women, if the case report indicated the pregnancy status. All opthalmia neonatorum and neonatal pnuemonia cases were individually verified for the demographic, treatment, diagnosis and provider data during this period of time.

Routine quality assurance reports were run at the local district reporting level. These were used to verify that all positive cases had an age, sex, and race identified (P. Moncreif, personal communication, June 30, 1999). These morbidity reports were in turn then reported to the Bureau of STD Prevention and Control (known as the Office of AIDS/STD/TB at that time). At the state level, scheduled quality assurance reports are run to identify outliers, any duplicate records, and contradictory diagnosis codes. An example of an outlier that would be a red flag: a greater number of positive laboratory test reports from an area that has reported a disparately smaller number of cases. It would be more usual to see the reverse pattern identified. Annually, morbidity line lists were produced and then forwarded to the district STD offices for verification of case numbers, age, race,

name, and diagnosis. Generally, the age and sex fields have a 98% completion rate, with race ranging from 80-85%. This difference is the result of absent race/ethnicity information from private providers. Each of the quality assurance components is applicable to the discrete study data set time period. This data set provided key variables for the final study database, and these are presented in Appendix A.

Congenital syphilis database. The congenital syphilis records are the sixth and final database from which study files were extracted. This database is managed much as the maternal and infant morbidity database above. However it was separate proprietary system created circa 1990 and not linked electronically to the maternal or infant case morbidity in the Sexually Transmitted Disease Management Information System (STD*MIS). The movement of information into this system differs from that of the morbidity system in one distinct way. All data entry for the 1996-birth cohort of congenital syphilis cases was done in the Bureau of STD, unlike the maternal and infant case morbidity that was entered at the local STD area offices. Additionally the data on each case was initially submitted on lengthy case worksheets. Bureau of STD personnel then confirmed the details of the mother's syphilis laboratory test results, her diagnosis, and treatment history. With this additional information the case determination was made as to whether or not the submitted congenital syphilis case report was indeed either a true clinical and laboratory confirmed congenital syphilis case, or a case that met the national surveillance definition for "probable" congenital syphilis (CDC, 1998a). The case determination for congenital syphilis applied to both live infants born to untreated or inadequately treated infected women and to syphilitic stillbirths. A positive feature of this database was the close scrutiny that each case received during the determination process. A limitation of this

database with its stand-alone design was the failure to directly link by computer the infant case congenital records to the maternal case history, laboratory tests, or treatment records. This weakness has been resolved in the 1998 STD*MIS system version with the development of an internal congenital syphilis module.

Methodological issues in the use of administrative databases

Teutsch and Churchill (1994) make recommendations regarding the management of databases to maintain the integrity and completeness. Among the issues that must be addressed are the credentials of data entry staff, updating of records, back-up of computer files, automatic data entry fields, e.g., today's date or today's age calculated from date of birth. Controlled system parameters and "must enter" fields are useful to ensure accurate spelling of common variables, e.g., county names, and validate data entry for completeness. No documented independent validation studies have been conducted on the data contained in any of these data systems and entered during the period spanning late 1995 to the middle of 1997, the timeframes for data-sets included in the study. However, routine production of quality assurance reports facilitate the identification and frequency of common errors, identify the appropriateness of the range of values entered, and assess the completeness of demographic data entry from each of the systems from which these data set were extracted.

Other published guidelines provide suggestions for the evaluation of surveillance systems like the STD maternal and infant case morbidity and congenital systems used in this study. Evaluation of a surveillance systems should include 1) description of the importance of the health event under surveillance, 2) description of the system, 3)

characterization of the usefulness of the data for decision making processes in public health, 4) evaluation of the actual system for attributes such as simplicity, sensitivity, and representativeness, 5) direct costs, and 6) recommendations (Klaucke et. al., 1998; WHO, 1997). No documented independent evaluation reflective of these guidelines has been conducted on the data contained in any of these surveillance systems.

Reliability of the information in each data sets utilized from which to extract study variables is an issue common to all of the systems. Herrmann (1985) compared self-administered to interviewer-administered questionnaires in a case controlled study for agreement and reported that consistently higher agreement levels for medical history with interviewer-administered questionnaires was observed. Harlow and Linet (1989) conducted a literature review of studies comparing data from questionnaires with information derived from medical records. Significantly high accuracy over extended periods of time was noted for each woman's recall of her pregnancy histories, childbirth experiences, and events. Less reliability was observed for menarche, menstruation, and menopause timeframes. All but one of the study data sets utilized interviewer-administered questionnaires and medical extraction followed by data entry into the data systems from hard copy records. The one exception, Healthy Start prenatal screen, is often completed by the pregnant woman, but may also frequently be interviewer-administered.

Definition of Study and Indicator Variables

The study variables used by this investigator were obtained from different data sets within the linked relational database. Dependent variables and independent indicator variables were created to support the calculation of crude odds ratios and the logistic regression analyses. Please see Table 3.

The list includes the following: alcohol use in pregnancy, alcohol use in the last two months, birth interval, body mass index group, chlamydia positive, gonorrhea positive, gestational age, high school graduate, history of past or current sexually transmitted disease, inadequate weight gain, low birth weight group by gestation, low birth weight, marital status, medical history, mistimed pregnancy, mother was low birth weight at birth, mother is of foreign birth, mother of black race, mother resides in a rural area, prenatal care indices, prior poor pregnancy outcome, smoked during pregnancy, smoked in the last two months, and stress identified in mother's life. All indicator variables used in logistic regression were coded with '0' for absence of, and '1' for the presence of the designated condition, risk or measure. Other variables were coded according to their use in the study analysis. Supportive syntax utilized for the indicator variables is contained in Appendix B. The dependent variables included low birth weight and low birth weight groups by gestational age. All other variables were used as independent variables in the calculation of crude odds ratios and for the logistic regression models. Due to the complexity of some variables, and their development from multiple database variables, more in-depth explanation follows.

Dependent variables: (Please refer to Table 3.).

Low birth weight (LBW) was defined as birth weight greater than or equal to 500 grams and less than or equal to 2499 grams. All live births and fetal death records without a recorded weight, a weight of less than 500 grams, or more than 5,500 grams (302 births/0.6%) were assigned to the "missing values" in the computations.

Table 3. List of All Variables Used in Analysis.

Dependent Variables
1. Low birth weight
2. Term low birth weight
3. Pre-term low birth weight
Independent Indicator Variables
1. Age < 18, > 40
2. Alcohol use from birth record
3. Alcohol use from Healthy Start screen
4. Birth interval short
5. Chlamydia positive
6. High school - no-
7. Gonorrhea positive
8. Inadequate PNC indices
9. Inadequate weight gain
10. Married – not
11. Medical history
12. Mistimed pregnancy
13. Mom foreign born
14. Mom LBW
15. Prior poor pregnancy outcome
16. Race of mother black
17. Rural residence
18. Smoking from birth record
19. Smoking from Healthy Start
20. STDs, past or current
21. Stressful life

Term low birth weight (TLBW) was birth weight defined as greater than or equal to 1500 grams and less than or equal to 2499 grams and gestational age equal to or greater than 37 weeks. Pre-term low birth weight (PTLBW) was defined as LBW with gestational age of equal or greater than 20 weeks and equal or less than 36 (Ventura, Martin, Mathews, & Clarke, 1996; Graf & Perez-Woods, 1992). LBW, PTLBW and TLBW were the dependent variables for the logistic regression models.

Gestational age was calculated from the date of birth and date of the last menstrual period reported on the birth certificate (Ventura, Martin, Curtin, & Mathews, 1999). Where the day of the month was missing the fifteenth was imputed (Buescher, Smith, Holliday, & Levine, 1987). Reported gestational age in weeks had a slightly narrower standard deviation (2.56) compared to that of estimated gestation (2.84). In addition, the skewness for the reported gestation was larger (1.07) compared to the skewness for the calculated gestation (0.42). When those births with computed gestational age less than 20 weeks and greater than 42 weeks (11.4%) were removed, the skewness was reduced even further to (0.37), with a histogram that presents a more normal curve. Given this information, the assumption was made that the calculated gestational age is more reliable since the calculated gestational age exhibited a more standard bell-shaped curve than reported gestational age. There may be bias in the reported gestational age data due to the fact that reported gestation is recorded after the birth has occurred and the size, weight, and appearance of the infant may influence the clinical estimate of gestational age. Some researchers have expressed concern that calculated gestation from the LMP date underestimates in the direction of pre-term deliveries (Kramer, McLean, Boyd, & Usher, 1988). There may also be recall bias associated with the calculated gestational age. The

last menstrual period date could be entered onto the birth or fetal death record based on either information contained in the prenatal records collected long before the birth and available at the time of the delivery, or on maternal recall. However calculated gestation is not as likely to be influenced by the birth outcome.

All live births and fetal death records without a recorded last menstrual period (LMP) or a LMP month with a value of more than 12 or less than 1, from which to compute the gestation,were assigned to the "missing values" category (12,557/6.4%). Additionally, following calculation, any record with a gestational age less than 20 weeks (79/0.2%) or more than 42 weeks (6,373/3.3%) was also assigned to the "missing values" in the computations.

Two other methods have been employed elsewhere but not in this study to address inconsistency in birth weight to gestation ratios. One method is a comparison of the calculated to the estimated with selection of the one most consistent with the reported birth weight. Another method has been to redistribute all records with inconsistent outlier values to the distribution observed in those with valid parameters.

Independent indicator variables: (Please refer to Table 3.).

Age at the time of delivery was calculated from maternal date of birth and incrementally grouped into < 15, 15-19, 20-24, 25-34, 35-39, 40-44, and ≥ 45 years for the initial analysis and calculation of crude odds ratios. For the logistic regression modeling, the maternal age variable was assigned a value of '1' for women younger than 18 and women 40 years or older, and a value of '0' for age 19 to 39 (Gjerdingen, 1992; Buescher, Taylor, Davis., & Bowling, 1993; Ketterlinus, Henderson, & Lamb, 1990; Rosenfeld, 1990).

Alcohol use in pregnancy was obtained from a field on the live birth certificate. When 'yes' is answered, a secondary part asks for the average number of drinks per week. This variable does not allow for identification of when, during the pregnancy, alcohol was consumed, or if the woman drank and then stopped drinking once she realized she was pregnant.

Alcohol use in the last two months was obtained from a field on the Healthy Start prenatal screen. This variable does not allow for clarification if the consumption took place prior to the onset of pregnancy, as might be the situation where a screen was conducted early in the first trimester. When considered alone, the information from this variable does not provide clear information on the quantity of alcohol consumed, or whether the woman drank throughout the pregnancy. Both of these variables are a crude measure of alcohol use in pregnancy and do not provide an accurate level of risk assessment or measurement.

Birth interval was created to capture information on the time from any prior event of pregnancy regardless of outcome, and the present birth. Many authorities have long espoused that a woman should ideally space births two years apart to allow their bodies to replace reserves and recover physiologically from the pregnancy and birth processes (Youngkin & Davis, 1994). Researchers in Utah recently defined a short inter pregnancy interval (IPI) as one that was less than 12 months based on a parallel study that demonstrated an increased association for adverse perinatal outcomes with IPIs of less than 12 months (Duncan, Nagle, Streeter, Bloemaum, & Tingey, 1998). This group calculated the IPI from the time between delivery dates of consecutive live-born infants and the gestational age of the most recent child. Another study conducted in Florida

examined the association between low birth weight and the interval between pregnancies, reporting that the LBW increases markedly at IPI of less than 9 months (Thompson, 1995). In the second study, the inter pregnancy interval was calculated from the date of the last menses and the date of the last live birth, both of which were taken from the birth record. This calculation was utilized for the indicator variable with a value of '1' given to those women with the designated risk of a birth interval less than 9 months.

Body mass index group was calculated in numerous steps based on the following formula: weight [kilograms]/height [meters]^2 (Abrams & Parker, 1990; Anderson, Anderson, & Glanze, 1994). Initially, the weight in pounds before pregnancy from the Healthy Start prenatal screen file was converted to kilograms. The height in feet and inches was then converted to height in meters. In the next step the weight in kilograms was divided by the height in meters squared to assign a body mass index value to each woman. The calculated score placed a woman in an underweight, normal weight, overweight, or obese category according to published standards for pregnancy BMI (Florida Department of Health, 1999).

Chlamydia positive and Gonorrhea positive were both taken from the Gen-Probe PACE2C® test results contained in the laboratory data file. Only those test results designated either positive or negative, were used in the analysis. All results designated indeterminate or unsatisfactory were assigned to 'missing' for clarity of interpretation.

High school graduate was calculated from information on the mother's highest level of education completed contained on the birth record, grouped as having not completed high school, having competed 12 years of education and as having completed more than 12 years. For the logistic regression analysis, women with an age of equal to or

greater than 18 years at the time of delivery and having less than or equal to eleven years of education completed were value of '1' for the designated risk of not having completed high school. While an age appropriate score was not assigned to younger adolescents, this variable does not 'penalize' a young teen for not yet having completed high school at the time of delivery, or place a younger adolescent within the risk category.

History of past or current STD was created to capture fragmented information contained in the multiple data sets. Due to distinctly differing rationales to record or not record any information related to a history of a recent past or present STD, all possible positive events were captured. However, a woman was only counted once if any field was positive for any STD event. A report of herpes in this pregnancy from the birth record was not included. 'Yes' responses were included from the following fields:

1) chlamydia positive or gonorrhea positive on either the mother's laboratory linked file or the infant's file;
2) a morbidity case report for the mother designating a condition of chlamydia, gonorrhea, pelvic inflammatory disease, primary, secondary or early syphilis;
3) a morbidity case report for the infant designating a condition of chlamydial opthalmia, gonorrheal opthalmia, chlamydial pneumonia, or congenital syphilis;

Inadequate weight gain was computed from the body mass index (BMI) group, gestational age in weeks and recommended weight gain ranges in pregnancy for each BMI group. Any woman not achieving the recommended weight gain was assigned a designator risk measure of '1'. (Florida Department of Health, 1999). See Appendix X for more detail on the applicable calculations.

Marital status was defined as married or unmarried.

Medical history for this pregnancy is a category reported on the birth record to capture any of the following sub-variables; diabetes, chronic hypertension, anemia (hemoglobin <10, hematocrit < 30), pregnancy-associated hypertension, cardiac disease, hydraminos, oligohydraminos, eclampsia, renal disease, acute or chronic lung disease, or hemoglobinopathy. Extensive literature exists linking these sub-variables with adverse pregnancy and birth outcomes. Isolation and linkage of each of these sub-variables was beyond the scope of this study. There is less or significantly conflicting information for other sub-variables such as like genital herpes, incompetent cervix, Rh sensitization and other/specified

Mistimed pregnancy Three fields on the Healthy Start prenatal screen file contain information on the timing of this pregnancy in response to the question "If you could change the timing of this pregnancy, would you want it a) earlier, b) later, c) not at all, or d) no change?" An answer of 'yes' to any of the first three fields designated a woman as at risk for a mistimed pregnancy in the indicator variable. Mistimed or unwanted pregnancies have been associated with increased risk of LBW and pre-maturity (Committee on Unintended Pregnancy, 1995). This group examined numerous studies and reported unadjusted odds ratios ranging from 1.2 to 1.4. The authors noted that if all unwanted pregnancies were eliminated there would be 7% less births, less than 2,500 grams among black women and 4% less among white women (Kendrick, 1990 as cited in Committee on Unintended Pregnancy, 1995). An evaluation of various population based surveys conducted in Florida suggests that the unintended pregnancy rate ranged from 43.04 % to 61.92% during 1993 among the women surveyed (Steele, 1995).

Mom LBW at birth was extracted from the Healthy Start prenatal screen question addressing the mother's recollection of the weight at her own birth. Yes was computed to a value of '1'.

Mother of foreign birth Limited information was available in the birth record regarding the woman's place of birth. Besides the 50 states, the record system supports acceptance of codes for a few other countries and United States territories: Puerto Rico, Virgin Islands, Guam, Canada, Cuba, Mexico, and "the remainder of the world". All women whose birthplace was coded to one of these were designated as foreign born. It was anticipated that this information might be useful in the analysis in light of studies that have demonstrated a decreased risk of LBW among black foreign born women and an increase among United States born women of black race. Similar findings have been reported from other studies in populations of Hispanic migrant women.

Mother of black race has been associated with an increased risk for LBW in many studies. For the purpose of analysis, black race was assigned from the mother's race field in the birth record. Less than 1% of women were of unknown race, while significantly higher rates of unknown or missing race were contained within the other files, e.g., 40.4% of birth records did not have a Healthy Start prenatal screen, and only 4.3% had race from the laboratory test file. Maternal race was grouped by black, white and other for the descriptive analyses. For the logistic regression, race was grouped by black and non-black.

Mother resides in a rural area. Conflicting information is available about the contribution of a woman's place of residence to LBW. Some literature suggests that urban residence may increase the risk of STDs and of LBW, rural residence may be protective. This variable was computed based on population of the mother's county of residence, and

whether she resided within or without the limits of her town or city. The county and city limits fields were from the birth record. The population parameters were assigned from the Florida 1999 Population Estimates provided by the Division of Economic Demographic Research, Joint Legislative Management Committee, 1998 Mid-Year Estimates.

Prenatal care indices were assigned to each record of '1' or '0'. This proved to be one of the more challenging variables to develop! The literature abounds with studies that report measures of adequacy of care and their association with birth outcomes. Most were developed for routine, low risk prenatal care and do not account for high risk pregnancies where more frequent visits would be recommended during the course of pregnancy (Stringer, 1998). While all published indices are used to measure a defined "adequacy of prenatal care" they actually count number of visits, and trimester of entry into care. None really achieve any assessment of the quality of care, the content of care, or the presence, absence or scope of particular care components. Several measures endeavor to adjust the expected number of visits to trimester of initiation, parity, and gestational age at birth. The GINDEX revised ACOG index of inadequate prenatal care utilization criteria and missing care was utilized to create a variable of "inadequate prenatal care indices." (Alexander & Kotelchuck, 1996; Alexander, Tompkins, Petersen., & Wesis, 1991). These indices were selected since syntax was available for reference, and because it most closely resembles the county health department standards for prenatal care initiation in the first trimester and the number of recommended visits. See Appendix B for the syntax and more detail.

Prior poor pregnancy outcome was computed from fields contained in the birth record (previous infant 4000+ grams, previous pre-term or small-for-gestational-age infant) and from the Healthy Start prenatal screen file (prior pre-term, prior LBW). A risk

value of '1' was assigned to any record with a 'yes' code in any of these fields sought. Neither data set clarified if the recorded abortions were spontaneous or induced; therefore, this field was excluded.

Smoked during pregnancy and smoked in the last two months, like the risk variables for alcohol, which do not allow for clarification that the use of cigarettes or other forms of tobacco use took place prior to the onset of pregnancy, were discontinued as a result of personal motivation or smoking cessation classes. Considered alone, the information from this variable also does not provide clear information on the number of cigarettes smoked each day or frequency of tobacco use throughout the pregnancy. Both of these variables, as with alcohol, provide only a crude measure of the risk associated with tobacco use during pregnancy. Smoking continues to be reported in the literature as having a strong association with LBW. Conversely, researchers report reduction in the risk for small-for-gestational-age births subsequent to decreases in tobacco exposure during pregnancy (Cnattingius & Haglund, 1997).

Stress identified in mother's life combines several potential psychosocial stressors that may necessitate some degree of adaptive or coping behaviors by the pregnant woman. A "yes" response to any of the following stress related life situation computed a score of '1' for a women for the purposes of this variable: 1) no insurance coverage, 2) problems keeping appointments, 3) moved more than three times in last 12 months, 4) felt unsafe, 5) someone in household goes to bed hungry, 6) physical violence, and 7) stress level of medium or high.

Methods of Analysis

Development of relational database .The preliminary step performed to support the analysis was the matching of the above-described administrative databases to create a single relational database. The birth and fetal death records were identified as the base file to which all other files were matched. This file was selected because it was the largest; it also offered a unique identifier for a linkage key. Each administrative database was sequentially matched supported by AUTOMATCH, as explained in more detail below (MatchWare Technologies, Inc, 1997). Once the "matched records" were identified a relational study database was created in ACCESS linked by the birth fetal death certificate number (Microsoft, 1997).

AUTOMATCH is a generalized record linkage system software that supports individual record matching, geographic coding, "many-to-one" matching single file grouping, and unduplication of records through probabilistic estimating techniques. This study utilized the "many-to-one" and the individual record matching functions of the software. Individual record linkage involves the use of two files, "A" and "B" to locate records that belong to the same individual despite missing or incorrect information. This allows one to use administrative files to find missing data and create a more comprehensive data set about individual persons. "Many-to-one" matching is similar to the individual record linkage but allows for matching of one set of independent records to any of the records contained in the other file (MatchWare Technologies, Inc, 1997).

Variables are selected for the match specifications based on reliability and statistical values and their distribution. Probability estimates are calculated for match (m) and unmatch (u) based on analysis of the frequency of occurrence. The more reliable a

variable, the higher the *m* probability value. Probability of *m* is the "probability that the field agrees given the record pair is a match." This is one minus the error rate of that field. The *u* probability is the "probability that the field agrees given the record pair is unmatched." An individual weight is computed for each comparison, and subsequently for normalization, a composite weight is computed for the sum of the field as a logarithmic value at base two of the ratio of *m* and *u*, e.g., log2 (*m*/*u*) (MatchWare Technologies, Inc, 1997).

Prior to attempting any record linkage the files must be standardized. For example records must be a fixed size, with fixed fields and of a standard flat ASCII or database type. Each data field that will be used for matching, blocking, and linkage must also be standardized. For example date fields must be in year-month-day order, e.g., 19990704. Missing values and zero values must be distinguishable below (MatchWare Technologies, Inc, 1997). Names are separated into surname, first name and middle initials.

The "many" tests to "one" patient (mother) matching sequence is described to better elucidate this phase of the analysis methodology:

1. Files A and B were evaluated separately for layout, fields were standardized, and data dictionary lists created to identify each variable name, size and location.

- The case morbidity files were selected for "File A" and the birth and fetal death records for "File B."
- This step was supported by use of SOUNDEX and NYSIIS, both registered software used to support record linkage, to standardize name, street1, street2, city, state, and zip on the case morbidity file. This was followed by standardization of father's name, mother's address, and mother's city on the birth fetal death record file.

2. Files A (case morbidity) and B (birth fetal death record) data dictionaries were compiled.
3. Matching specifications were prepared for files A and B, then compiled. Variables are selected for the match specifications based on reliability and statistical values. Probability estimates and cutoff values were calculated for matched and unmatched pairs.

- Initially the "*m*" and "*u*" are guessed or assigned by the user. Subsequently, the system will estimate the probabilities of each when the first pass is run. The decision can then be made to adjust the model and the cutoff values. A high value would be initially given to either a critical field or a known reliable, depending on the matching specifications and the quality of the data.

4. Indexes for match parameters in each pass were created as described, with altogether five blocks employed. The blocking of variables allow for grouping sets of records for comparison, e.g., group all with the same last name, to compare to sex on the first pass and age on the second. Two of the five blocking algorithms follow:

- Block 1 on mother's last name, then first name. The STD exam date specified to be 280 days prior and 180 days after the infant's date of birth. Next mother's date of birth month was compared to the case file date of birth month. The next blocking specification was by birth address, mother's race, ethnicity, and social security number.
- Block 2 began on the social security number followed by the mother's year of birth. Again, the STD exam date was specified to be 280 days prior and 180 days after the infant's date of birth. The mother's date of birth month was compared to the case file date of birth month. Last, the mother's last name to case morbidity last name by

NYSIIS and SOUNDEX, and the same for first name, street address, city, county, zip, and race.

5. A frequency analysis is prepared on both files. This allows for a visual inspection of the probabilities, blocking, and linking variables.
6. Clerical review to inspect the *"m"* and *"u"* and blocking specifications is conducted. This guides potential editing of the specifications and continuation of the number of passes to employ.

- At this step, matching probabilities were revised for both files and the automated match was initiated utilizing five passes on different blocking algorithms with clerical reviews conducted at each pass. At each review, new cutoff values were assigned based on the amount of residual unmatched records.
- At each pass and clerical review, the matched records, clerical review cases, and duplicates are removed to prevent repeat matching of a record in a subsequent pass.

7. Extract specifications were prepared for the output files.

- After this, the case morbidity file was imported into ACCESS for "grooming" in anticipation of the relational database development.

Descriptive analysis. Descriptive analysis was conducted on demographic variables, prevalence of sexually transmitted infections, and other select variables in the study population. Sub-populations of county health department clients, specifically women giving birth to LBW, TLBW and PTLBW infants was then examined according to the selected variables and presence or absence of a positive test result for chlamydia infection by frequency, distribution, and consistency between the linked data sets. Bi-variate cross tabulation was conducted between the dependent variables (LBW, TLBW, and PTLBW)

and the indicator variables. The results of these cross tabulations were entered into a spreadsheet to test for significance and calculate the unadjusted odds ratios for each indicator variable. Uni-variate and multivariate analysis was supported by Statistical Package for Social Sciences 9.0 (SPSS Inc, 1999). Additionally, bi-variate tests for significance and calculation of unadjusted odds ratios was supported by Microsoft Excel 97. Statistical significance was sought at the p value ≤ 0.05 and 95% confidence intervals.

Logistic regression. Multivariate analyses of selected variables was used to further explore the association between LBW, chlamydial infection, and to select potentially confounding variables. Variables found statistically significant in the bi-variate analysis were placed into various selection models: enter, forward stepwise selection, and backward stepwise elimination. Variables initially entered into the desired models are removed based on different statistical tests: Wald, change in likelihood or conditional statistic. Initial exploratory examination of the variables with the available logistic models and use of the various statistical criteria suggested that the backward elimination model utilizing the likelihood-ratio test was the most suitable for use in the study sample. Additionally, the backwards elimination model allowed for observation of which variables were eliminated at identified levels of significance, and provided useful insight into the discussion on the findings for sub-groups within the study sample in relation to the study question. All analysis was supported by Statistical Package for Social Sciences 9.0 (SPSS Inc, 1999). Statistical significance was sought at the p value ≤ 0.05 and 95% confidence intervals.

Inclusion and exclusion criteria

For the preliminary descriptive analyses all records in each relational database table were included to determine the sample distribution. These records include: the birth fetal death records, STD case morbidity for mothers and infants, the Healthy Start prenatal screening records, the laboratory test database for mothers and infants, and the congenital syphilis case reports. At the second step, descriptive analyses were conducted on the final linked study sample. The study sample was limited to all women and female adolescents who initiated prenatal care through county health departments and met the following inclusion criteria: pregnant, with a social security number and date of birth, and a matching birth fetal death record registered in the Florida Vital Statistics for 1996. The sub-populations of women and adolescents who delivered low birth weight, term low birth weight, and pre-term low birth weight infants were then examined for distribution, similarities, and differences and compared to similar sub-populations in the full birth and fetal death records file.

Exclusion criteria were applied only to the extracted study sample. The study sample was extracted with the following exclusion parameters: 1) non-county health department client as identified from the Healthy Start data file variable "CHD provider"; 2) multiple-gestation births; and 3) those births identified as delivered by Cesarean section. (Keith, Papiernik, Keith,, & Luke, 1995; Ventura, Martin, Mathews,, & Clarke, 1996). The exclusion criteria decision for each relate to the scope of the study question(s). The investigator sought to examine women served in county health departments with a chlamydia test result. No laboratory information is available within the linked database for the majority of women, those served by private providers.

Assumptions

The reliability of information contained in the birth record files has been discussed in the literature (Buescher, Taylor, Davis., & Bowling, 1993). The investigator had no reason to assume that the completion accuracy of the records used in this study would be any less than that of other records not selected in the matching process.

Limitations of the Study Design and Methodology

This study had three primary limitations. The sample population, while representative of pregnant women attending county health departments in Florida, may not be representative of all pregnant women who delivered in the state during the study period. The county health departments enrolled 30,234 women into prenatal care during 1996. However, not all would have delivered during the calendar year, and some would have experienced a pregnancy or fetal loss as well. This number represents 15.7% of all births and fetal deaths recorded in the state during that same year. The study sample examined extracted the records of 14,002 women who initiated their prenatal care through the county health department for the logistic regression modeling. The number may represent approximately half of those who were provided prenatal care in the county health departments during that time period. The rate of first trimester entry was very similar for both groups of county health department women (62.8% during the calendar year and 61.4% for the study sample). The power of some independent variables was limited by the sample size, e.g., chlamydial and gonorrheal infection.

The second significant limitation was loss of data and, consequently, potential strength of the laboratory test variable, through the loss of months of information from the

laboratory database. Failure of hardware contributed to corruption of data files. Months of data for 1996 were permanently lost secondary to an inadequately designed archival system. This factor, combined with the staged implementation of the computerized laboratory system, reduced the number of laboratory test results available for matching.

The third limitation relates more to the study design. The data utilized in this study were gathered retrospectively from existing databases rather than prospectively in a specifically designed study. As a result, undetected bias may be present in the data. Undetected bias may also be present in data as a result of the matching processes and incompatible demographic data that precluded complete matching of records.

Each of the study database files was developed independently of the others. As a consequence, there are significant differences that hampered the construction and the subsequent analyses. Some differences could be remedied relatively easily, like the standardization of certain fields before the matching processes began. Other initially important differences in the data quality added impediments to the analysis stage. For example, the Department of Health presently supports three different sets of county coding within the various database systems.

Examination of the distribution of counties from which patients were included at the preliminary analysis of the case morbidity file, suggested that there were an excessive number of syphilis cases from several rural counties. A close scrutiny showed that the city, zip code, and clinic where services were provided were all located in Dade County. The codes used were 'correct' for the county health department system, but not for the STD*MIS system, yet both systems accept the numbers as valid. A similar observation

was made on the laboratory file, where Vital Statistics system codes were used in place of the county health department codes that should have been used in that database system.

Another example is exemplified by the activities related to matching the congenital syphilis case records. All congenital syphilis case records were for infants born in Florida during 1996. A birth record should have been linked to each one. However, not all cases were successfully linked. Many of the linked cases required extensive desk audits to identify the discrepant spelling of names, transposing of first and middle names, etc. In some cases reference to the original case worksheet was required. While the congenital syphilis event was not integral to the original research question, the study findings clearly suggest that the total burden of sexually transmitted diseases are a significant factor in the increased risk of low birth weight among this population. Therefore a higher match rate for these files was desirable.

Data quality was at times affected by computer system design flaws. This was sometimes only detected in the analysis stage. For example, the Healthy Start prenatal screen databases often do not have build-in restrictions to limit the valid entries in many fields. As a result, many fields have a certain percentage of aberrant responses that required tedious gleaning of the field and decisions on how to handle these and missing replies at each stage of analysis.

Strengths of the Study

Development of the relational database through the stringent processes employed provided an opportunity to extract quality data from multiple files simultaneously with assurance that the information pertained to the same individual or case. Additionally, the linkage supported the creation of complex variables for the analysis using fields from several files. The matched files also allowed for scrutiny of some demographic fields to ascertain the level of concordance between databases. Finally, development of this database has provided a source of data that will support further analysis and studies, as well as a model for similar studies on this or other topics in the future.

CHAPTER 4
RESULTS

In this chapter the results of linking the respective databases, the descriptive analyses, results of research questions, and statistical significance of the findings will be presented. Some additional unanticipated findings of interest will be presented at the close.

Results of Linking the Respective Databases

The original study design included all of those data sets included in the present analysis: birth and fetal death records, Healthy Start prenatal screen, maternal and infant sexually transmitted case morbidity, and maternal and infant chlamydia laboratory test results. The study would also have included the following: 1) geocoding of records by census tract and income from the 1990 United States Census; 2) county health department service codes; and 3) Medicaid service and pharmacy records. Many individuals contributed extensive hours over the course of two years to clean and prepare the files for linkage within this relational database. Each step of the file preparation, matching processes, and quality assurance checks required more time than anticipated or scheduled for in the study timeline. Due to study completion time constraints, it was decided to conduct the analyses without the development of those linkages that were still pending by July 1999, or the information that those data sets contained. The final three components

remain available and will be completed at a later date to support additional analyses and research questions. The final steps in the analytical progression are presented in Figure 4 below.

The 1996 birth and fetal death record database contained 190,497 births and 1,501 fetal death records. Through the methodology described in the previous chapter, each of the other respective databases were consecutively matched and linked by the respective birth or fetal death record number to the individual case records. Different time parameters were established for the respective files. For the files containing information about the potential birth mothers, the time spanned March of 1995 through March of 1997. This time span theoretically allowed for capture of information relative to the prenatal period of the earliest birth in January 1996 and for a period of 90 days post-partum for deliveries that occurred at the end of December 1996. For the files containing information for infants born in 1996, the time span was from January of 1996 through June of 1997. This time span theoretically allowed for capture of information relative to the actual birth and for a period of 180 days post-delivery. Additional quality assurance was conducted within SPSS subsequent to the Automatch process to ensure that each individually matched record did not exceed the established time parameters.

From the laboratory database of 108,592 laboratory records meeting the time and gender parameters established, 27 records were matched to individual infants and 8,334 to individual mothers. This successfully linked only 4.3% of the mother's test records and 0.00227% of the potential infant records. Very stringent parameters were maintained throughout the Automatching process. These may have contributed to the lower rate of

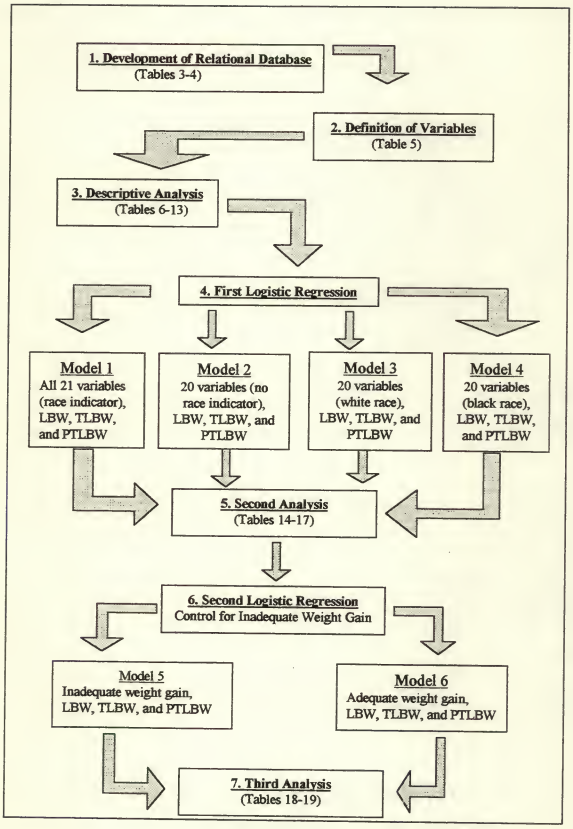


Figure 4. Primary Steps in Research Analysis

match. However, it is believed the rate reflects the inconsistencies of demographic data between different files. For example, many infants are not recorded with the same last name in the early months, or may be addressed by the mother or guardian with what is actually the middle name. As a result, this name may be used to requisition a laboratory test or entered onto the medical record from which the morbidity case information may have been extracted. Of the 126 infant morbidity cases relative to the parameters for a 1996 birth date, 110 were linked to a birth record (0.10%). From the 3,745 morbidity records meeting the initial matching parameters 317 (0.2%) were linked to mothers, These included 308 to birth records and 11 to fetal death records.

The Healthy Start prenatal screen database contained 191,333 records spanning the period from 1995 through 1997. Of these, 59.6% (113,771) of the screens were linked to a birth record and 44.3% (665) to a fetal death record. In total, no screen was matched to more than forty percent of birth and fetal death records for the live births and fetal deaths that occurred during 1996. The total number of records from each database is presented below in Tables 4 and 5. The overall percent of records successfully linked is very low for the STD maternal and infant case morbidity, the laboratory test database and the congenital syphilis database.

Besides changing the scope of the data content available for analysis, halting the data base construction also required a change in the methodology for extraction of the final study sample. Originally, the study design included the county health department service codes in order to identify all women who were health department patients for inclusion at the first step of descriptive analysis. Inclusion and exclusion criteria of those women who were both pregnant and had a linked chlamydia laboratory test would have

been applied at the third step, the logistic regression modeling. Another option would have been to select all women who had a laboratory test result for chlamydia with the

Table 4. Total Records Linked to the 1996 Birth and Fetal Death Records.

Birth Fetal Death	Healthy Start Prenatal Screen	Maternal Lab Test	Maternal Morbidity	Infant Lab Test	Infant Morbidity	#	%
Linked	-	-	-	-	-	76,959	40.1
Linked	Linked	-	-	-	-	106,336	55.4
Linked	Linked	Linked	-	-	-	7,829	4.1
Linked	Linked	-	Linked	-	-	162	0.1
Linked	Linked	Linked	Linked	-	-	25	0.0
Linked	Linked	-	-	-	Linked	40	0.0
Linked	Linked	-	Linked	Linked	-	16	0.0
Linked	Linked	Linked	-	Linked	-	5	0.0
Linked	Linked	-	-	Linked	-	10	0.0
Linked	Linked	Linked	-	Linked	-	13	0.0
Linked	-	-	Linked	-	-	88	0.0
Linked	-	Linked	-	-	-	461	0.2
Linked	-	-	-	-	Linked	24	0.0
Linked	-	-	Linked	-	Linked	25	0.0
Linked	-	-	-	Linked	-	4	0.0
Totals:							
191,998	**133,771**	**8,334**	**317**	**27**	**110**	**191,998**	**100%**
100%	**69.673%**	**4.341%**	**0.165%**	**0.014%**	**0.057%**	-	-

assumption that all specimens sent to the Bureau of Laboratories would belong to county health department patients. While in the vast majority of cases this would be accurate, there was not a variable field to confirm that this was indeed true within the laboratory database. A program code was assigned to 90.3% of the laboratory tests. Of these 68.7% were for prenatal patients, 2.3% for STD, and 17.6% were from family planning clinics.

Additional calculations could have been performed to identify if the test was

collected during the pregnancy. However a third option existed to identify the women as county health department patients. This was the provider code contained within the Healthy Start prenatal screen data fields. This method was selected to identify the records

Table 5. Study Sample Records Linked to the 1996 Birth and Fetal Death Records.

Birth Fetal Death	Healthy Start Prenatal Screen	Maternal Lab Test	Maternal Morbidity	Infant Lab Test	Infant Morbidity	#	%
Linked	Linked	-	-	-	-	9,241	66.0
Linked	Linked	-	Linked	-	-	19	0.1
Linked	Linked	Linked	-	-	-	4,702	33.6
Linked	Linked	Linked	Linked	-	-	17	0.1
Linked	Linked	-	-	-	Linked	8	0.1
Linked	Linked	-	Linked	-	Linked	2	0.0
Linked	Linked	Linked	-	-	Linked	1	0.0
Linked	Linked	-	-	Linked	-	2	0.0
Linked	Linked	Linked	-	Linked	-	10	0.1
Totals:							
14,002	**14,002**	**4,730**	**38**	**12**	**11**	**14,002**	**100**
	100%	**33.7809%**	**0.2714%**	**0.0857%**	**0.07856%**	-	-

of women who received county health department prenatal services for sample extraction. There are differences in the odds ratios, confidence intervals and p values. It is possible that inclusion of all women with positive test results for chlamydia would have changed the findings in some way.

The methodology outlined in Chapter 3 was used to direct the linkage of records. It was stringent and time consuming in order to achieve the level of accuracy attained. The cut-off points for each step in the AUTOMATCH processes were maintained and as a result the time required for visual audits on decision to include or exclude records that

remained in the residuals contributed further to the time involved in overall matching of databases. In the process, this investigator frequently reviewed and checked the level of the matches achieved. This was a key aspect, for at these times, errors in matching parameters were identified or questions raised that assisted in improving the level of matches.

Descriptive Comparison of the Relational Database and Study Sample

The final sample extracted for the purposes of examining the research question represents 7.3% of the births and fetal deaths that took place during 1996. In some aspects, the two samples are very similar, in others, markedly different. Much of the descriptive comparison is presented in several tables for quick scrutiny. First a general overview of select similarities and differences will be presented. This will be followed by a more in-depth review of some more focused findings. It is important to temper any conclusions drawn about the similarities or differences between the two groups with the information because only 60% of the statewide sample (all births and fetal deaths for 1996) were linked to a Healthy Start prenatal screen. Therefore only 60% of the birth and fetal death records could also have data fields taken from the prenatal screen. In contrast 100% of those in the study sample were linked to a prenatal screen and had all of the corresponding data fields. Additionally, most records in the study sample also had a valid field from the Healthy Start prenatal screen database for the variables utilized. Therefore only 'valid percents' are presented in the descriptive tables were applicable for those variables with missing Healthy Start prenatal screens. The same principle was applied to variables from the laboratory and case morbidity records as even fewer records were

linked to laboratory tests or case morbidity records. This disparity reflects that 40% of women who delivered in 1996 did not receive a Healthy Start prenatal screen, and that only records for with a Healthy Start prenatal screen that indicated they had initiated care at county health departments were selected for the study sample.

The actual percent of women who were both offered and accepted prenatal screening, and delivered a live infant or experienced a fetal death during 1996 is unknown for comparison. During 1995 to 1997, the percent of women who were both offered and accepted prenatal screening ranged from 67.5% to 70.6%. This number includes women who were screened during their pregnancy for those time periods, but does not necessarily indicate that the woman delivered during the same 'year' that they received the prenatal screening.

Seventy-five percent of births or fetal deaths occurred to women of the general population between the ages of 20 and 34 years. Please refer to Table 6. In comparison a similar proportion of the 1996 births or fetal deaths occurred to a younger segment of women in the sample population; 74% between the ages of 15 and 30 years. The 'downward' shift to a younger age is reflected in the sample where the proportion with age at delivery between 15 and 19 years is more than double the corresponding proportion in the database. The distribution of age and race indicated that twice as many of the 129 women 14 or less years of age were of black race/ethnicity (data not shown). Twice as many were of white or other race/ethnicity for the 15-19 year old group, as were those in the 35 to 44 year old groupings. Race was evenly distributed among women between the ages of 20 to 34 years; three quarters were of white race/ethnicity.

Table 6. Comparison of Select Demographic Variables Between Relational Database and Study Sample.

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
TOTALS	191,998		14,002	
	#	**%**	**#**	**%**
Age at delivery				
≤ 14	634	0.3	129	0.9
15-17	9,459	4.9	1,708	12.2
18-19	15,279	8.0	2,408	17.2
15-19	24,738	12.9	4,116	29.4
20-24	46,454	24.2	5,008	35.8
25-29	50,973	26.5	2,633	18.8
30-34	44,089	23.0	1,399	10.0
35-39	20,639	10.7	590	4.2
≥ 40	4,288	2.2	127	0.9
Educational level				
< High school	40,906	21.6	6,287	44.9
High school	67,274	35.0	5,333	38.1
> High school	82,180	42.8	2,213	15.8
Married – yes	124,314	67.7	5,506	39.3
Prenatal Provider				
CHD	17,162	8.9	14,002	100
DOH contract	9,119	4.7	n/a	n/a
Private	46,689	24.3	n/a	n/a
Insurance				
HMO	23,993	12.5	356	2.5
Medicaid	43,450	22.6	9,684	69.2
Other	4,424	2.3	123	0.9
None	18,315	9.5	3,807	27.2

Table 6. Continued.

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
TOTALS	**191,998**		**14,002**	
	#	**%**	**#**	**%**
Trimester of entry[1]				
1st	116,328	43.1	8,602	61.4
2nd	51,099	20.2	4,351	31.1
3rd	12,189	4.8	1,012	7.2
Method of delivery				
Vaginal	149,304	77.8	-	-
Cesearean section	41,949	21.9	-	-
1st pregnancy - yes	62,314	24.1	5,204	37.2
Mother Hispanic - yes	36,001	18.8	3,039	21.7
Mother foreign born - yes	46,422	24.2	3,392	24.2
Mother's race				
Black	42,906	22.3	4,217	30.1
Other	4,652	2.4	293	2.1
White	144,197	75.0	9,492	67.8
Infant's race				
Black	45,935	23.9	4,556	32.5
Other	5,499	2.9	335	2.4
White	140,341	73.1	9,111	65.1

[1] Represents the Healthy Start variable.

While more than two thirds of women statewide were married at the time of delivery, a little more than one third in the sample were married. More than twice as many mothers had not yet finished high school in the sample while a similar distribution was

noted for those having completed 12 years of school. No information is available in the birth and fetal death records regarding the percent of women who did not graduate, and then went on to receive a GED.

All women in the study sample received their prenatal care from the county health department (CHD), while 8.9 percent of the general population were identified as having received their care at the CHD and 24% received their prenatal care from a private provider. Based on the information from the linked prenatal screens, Medicaid was the source of insurance coverage for more than two thirds of women in the study sample, and slightly more than one third for those in the general population. More than a quarter had no insurance coverage in the study sample at the time the screen was completed. Please refer to Table 6.

There were two variables available to measure the percent of women initiating care in each trimester of pregnancy. The first option and one field common to all records, but not necessarily completed, is from the birth and fetal death record: "the month prenatal care began." The actual trimester of entry date must then be computed from the date in this field and the reported date of birth or death. It is possible that maternal recall bias may affect the accuracy of this date. This investigator did not perform this computation within the context of this study. However, the Office of Vital Statistics (1997) reported that 82.3% received prenatal care in the first trimester. Among adolescent females aged 15-19 years, 6.3% received no prenatal care or not until the third trimester, compared to 81% of those under age 15 years.

The second option to identify trimester of entry into care was contained in the Healthy Start prenatal screen field: "Trimester of pregnancy at first prenatal visit." This

field immediately follows the last menstrual period and calculated estimated date of delivery. It is completed during the prenatal care period when the prenatal screen is offered and not likely to be associated with recall bias. However, it most likely is completed prior to ultrasonic verification of gestational age. Based on this second option for trimester of entry 61% of the study sample initiated care in the first trimester while only 43% were identified as entering care in the first trimester for the general population (valid percent based on Healthy Start variable). This finding is a marked difference from official reported rates and is presented in Table 6.

For all births, 77.8% were delivered vaginally and 21.9% by Cesarean section. Only those with a vaginal delivery were included in the study sample, due to exclusion of those experiencing a Cesarean section. The Cesarean section rate is slightly higher than the national rate of 20.7% and significantly higher than the rate for the total county health department population (17.3%). One quarter of the general population and more than one third of the study sample were identified as pregnant for the first time.

Nearly one fifth of the women in the study sample were identified as being of Hispanic ethnicity, a slightly lower percentage than in the general population. Ethnicity is a very misleading category in this database. Only eight "ethnic" options are allowed for data entry. These include 1) non-Hispanic, 2) Mexican, 3) Puerto Rican, 4) Cuban, 5) Central or South American, 6) other, 7) Haitian, and 8) unknown. Hence ethnicity in this data set literally indicates membership in some broad grouping of Hispanic ancestry, ranging from the Caribbean though Central and South America.

Close to two thirds of the study population were of white race compared to three quarters of all women. Of interest was the subtle shift in identified race for the infants. In

both groups there were slightly more infants of black race. Both populations had a similar percent of women who were foreign born. The percent reported as 'other' does not make up this difference. The birth and fetal death record coding instructions assign black race to all children born of black mothers except when the father's race is reported as Asian or American, then the child is assigned the particular race code for the father's country of origin. In the case of infant's for whom the father's race is unknown, the child is also assigned black race from the mother. Please refer to Table 6.

In categories of pregnancy timing for those records with a Healthy Start prenatal screen, women generally reported less dissatisfaction with the timing of their pregnancy, yet significantly fewer stated that the timing was acceptable. Please refer to Table 7. This variable is markedly affected by the 30% who declined to answer the question altogether, even though a screen was linked. Only one third as many women in the general population were identified with a medical history. Twice as many women reported having been themselves of 5.5 pounds or less at birth. More than twice as many women in the sample reported a prior poor pregnancy outcome. This is interesting considering that the overall rate of low birth weight was lower for the study sample than observed for the combined 1996 birth and fetal death records (6.9% compared to 8.1% respectively). This pattern was also noted for the proportion of fetal death records, with 0.78% observed in the relational database and 0.63% in the study sample.

Marked differences were observed for body mass index between the two groups, most likely the result of missing values on this variable for the larger group. Forty percent more women were calculated to have a low body mass index among the larger group.

Table 7. Comparison Between Relational Database and Study Sample of Selected Variables Used in Combination to Create Independent Indicator Variables for the Logistic Modeling.[1]

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
TOTALS	**191,998**		**14,002**	
	#	**%**	**#**	**%**
Timing of pregnancy				
Earlier	4,348	3.8	672	4.8
Later	25,187	22.0	5,142	36.7
Not at all	7,659	6.7	1,452	10.4
Timing is okay	40,853	35.7	6,699	47.8
History of medical complications	6,923	3.6	1362	9.7
Mother LBW at birth - yes	8,251	4.3	1,376	9.8
Body mass index				
Low	51,551	35.7	6,545	25.3
Normal	39,070	27.1	6,564	46.9
High	9,145	6.3	1,159	11.5
Obese	14,670	10.2	2,334	16.7
Prior poor pregnancy outcome	16,963	8.8	2,761	19.7
Plural birth	5,106	2.6	-	-
Resides outside of city limits	61,366	32.0	4,356	31.1
Stressful life questions				
Difficulty keeping appointments	5,800	5.1	1,714	12.2
Moved > 3x in 12 months	7,745	6.8	1,882	28.8
Feels unsafe	3,461	3.0	693	53.7
Hunger	2,492	2.2	711	17.3
Physical violence	4,871	4.3	1,143	4.8
Stress level low	22,121	19.5	4,032	36.7
Stress level medium	42,989	37.6	7,515	10.4
Stress level high	12,997	11.4	2,429	47.8
Chronic illness	6,818	6.0	1,354	9.7

Table 7. Continued.

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
Totals	**191,998**		**14,002**	
	#	**%**	**#**	**%**
Alcohol/drugs/tobacco use				
Alcohol – birth record	1,700	0.9	158	1.1
Alcohol – healthy start	11,933	10.4	1,910	13.6
Tobacco – birth record	23,524	12.3	2,871	20.5
Tobacco – healthy start	19,401	10.1	4,114	29.4
Sexually transmitted infections[2]				
Mom – chlamydia positive test	437	0.2276	285	2.0354
Mom – gonorrhea positive test	103	0.0537	51	0.3642
Mom – pelvic inflammatory disease	16	0.1536	3	0.0214
Mom – all syphilis	295	0.0015	35	0.2500
Mom – herpes	2,396	1.2479	96	0.6856
Infant – chlamydia positive test	1	0.0005	-	-
Infant – chlamydia opthalmia	37	0.0193	5	0.0357
Infant – gonorrhea opthalmia	4	0.0021	-	-
Infant – chlamydia pneumonia	2	0.0010	1	0.0071
Infant – congenital syphilis	67	0.0349	5	0.0357

[1] Some variable values do not total to 100% due to missing values in records.
[2] These variables at four decimal places to better illustrate that the event "did" occur.

In contrast, more than half as many in the study sample were of normal body mass index. Twenty eight percent of the study sample were of high or obese body mass index and sixty-one percent less were calculated to have an obese body mass index. Twenty four percent of black women were underweight in the study sample compared to 27.5% of white women (data not shown). One third again as many black women (21.2%) were obese as white women (14.7%). Both race/ethnicity groups were similarly distributed for

normal body mass index (whites 47.5% and blacks 45.4%). Ten percent of white women and 13% of black women were of 'high' body mass index.

Life stressors were among the questions used to solicit information about the level of stress and psychosocial problems in women's lives. Those in the study sample reported life stressors at a significantly higher rate than those in the general population. Please refer to Table 7. The only exception to this question was a medium stress level reported more than three times more frequently among the larger group that delivered during 1996.

The reported use of alcohol as recorded from the birth record, was very low and similar to the percent in the study sample. In contrast, alcohol/drug use from the Healthy Start field was reported about one third more often among women in the study sample. It is difficult to compare these two fields and make any inference regarding validity about the marked difference due to the different way in which the question is posed. Please refer to Table 7. On the birth and fetal death certificate, the mother is asked if she "used alcohol during this pregnancy." In the Healthy Start prenatal screen encounter, the question asked is: "In the last two months, have you used drugs or alcohol?" (including beer, wine, mixed drinks). While any comparison regarding these two database fields is problematic, the ten-fold difference suggests one of them is very unreliable and is subject to both recall bias and the skills of health care providers to elicit complete alcohol and drug use histories. It is unlikely that only among women who received a Healthy Start prenatal screen have alcohol and drug use associated with pregnancy. Tobacco use based on the Healthy Start prenatal screen variable was higher in both groups than for the same group from the birth record, and twice as much in the study sample. (Again this field is omitted from the fetal death record.)

Additional information is contained in the relational database that was useful in establishing an overall understanding of the population from which the study sample was extracted. Some of the more notable are included in the next chapter regarding sexually transmitted infections. Other data, while vast and of enduring interest, is alas, beyond the scope of this study and the limits of time accompanying it.

Descriptive Comparison of the Dependent and Independent Variables

Three dependent variables were used for the bivariate and logistic analyses. A comparison of these and the independent variables for both the general population and the study sample are presented in Tables 8 and 9. The study sample had a lower rate of low birth weight than that of the total birth and fetal death group (6.9% and 8.1% respectively). This number differs from the published rates in two ways. First it includes the weights of fetal death records linked to the birth records. The weight of recorded fetal deaths is not published in the annual state report on population, births, deaths, marriages and dissolutions of marriage (Office of Vital Statistics, 1997). Second, it is possible that some difference may result from the commuted dependent variables. The parameters are presented in Table 8 and in the definitions presented on prior pages. The percent of pre-term low birth weight is also lower in the study sample (3.5%) compared to the statewide low birth weight rate (4.8%).

Table 9 presents a comparison of the distribution of the created indicator variables between the total relational database group and the study sample. Definitions and descriptions of the calculations for these variables appear on pages above and in the syntax presented in Appendix B.

Table 8. Comparison Between Relational Database and Study Sample of Records Identified for Use as the Dependent Indicator Variables.

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
Totals	**191,998**		**14,002**	
Dependent Indicator Variable	**#**	**%**	**#**	**%**
Low birth weight (500 - 2499 grams)	15,437	8.1	963	6.9
Term low birth weight (1500 –2499 grams and ≥ 37 weeks)	4,483	2.4	355	2.6
Pre-term low birth weight (500 – 1499 grams and ≤ 36 weeks)	9,001	4.8	478	3.5

Consistent with the age distribution in the two samples presented in Table 4, a higher percent of young women were captured in the age indicator for the study sample. The computed inadequate weight gain is nearly one third higher in the study sample, 22.1% compared to 14.6%. The differences between both groups for the prenatal care indices would suggest that while more women from the study sample entered prenatal care in the first trimester they may not have met the required number of visits for gestation as did women in the relational database.

Significantly more women in the study sample did not complete high school. However the coding on this categorical indicator variable placed those under 18 years who had not yet completed high school into the same group as those over 18 years who did complete high school. Hence the younger distribution of the study population therefore did not contribute to the increase percentages, and this finding represents those who were over 18 years of age but had not completed high school at the time of the birth event.

Among those women over 18 years of age who did not complete high school, 71.7% were of white race/ethnicity.

Significantly more women were unmarried in the study sample (60.6%) as compared to 35.2% of those in the larger group. An interesting finding was the different distribution for short birth interval. However, this would be consistent with the observed older age distribution of the relational database, marital status and more opportunity for conception. More than two and a half times as many women in the study ample stated their pregnancy was mistimed. Even with the removal of Cesarean section deliveries it was interesting to observe that the history of an event of a prior poor pregnancy outcome was more than twice that of the larger group. The most marked difference between the two groups was that nearly all women in the study sample identified something in their lives that would suggest that their lives were stressful. The percent of women residing in rural areas was higher for the study sample, 38.2% as compared to 34.9%.

Alcohol use reflects the frequency presented in Table 5 as do the remaining other independent variables for the two groups e.g., tobacco use, black race, mother foreign born, chlamydia and gonorrhea positive, medical history, and mother low birth weight herself.

Bivariate Analysis

Each of the dependent variables was examined for potential associations with all of the independent variables at the 95% confidence level. Odds ratios and p-values were calculated for the independent variables to predict the probability of the occurrence of LBW, TLBW or PTLBW in association with each designated risk or measure. The

Table 9. Comparison Between Relational Database and Study Sample of Records Identified for Use as the Independent Indicator Variables.

	Relational Database		Study Sample	
Births	190,497		13,914	
Fetal Deaths	1,501		88	
Totals	191,998		14,002	
Independent Indicator Variable	**#**	**%**	**#**	**%**
1. Age < 18, > 40	12,929	6.7	1,909	13.6
2. Alcohol use from birth record	1,700	0.9	158	1.1
3. Alcohol use from Healthy Start	11,933	6.2	1,910	13.6
4. Birth interval short	41,501	21.6	2,502	17.9
5. Chlamydia positive	437	0.2	285	2.0
6. High school - no-	99,755	52.0	9,955	71.1
7. Gonorrhea positive	103	.01	51	0.4
8. Inadequate PNC indices	89,362	46.5	7,268	51.9
9. Inadequate weight gain	27,985	14.6	3,100	22.1
10. Married – not	67,556	35.2	8,491	60.6
11. Medical history	6,923	3.6	1,362	9.7
12. Mistimed pregnancy	37,194	19.4	7,266	51.9
13. Mom foreign born	46,422	24.2	3,392	24.2
14. Mom LBW	8,251	4.3	1,376	9.8
15. Prior poor pregnancy outcome	16,963	8.8	2,761	19.7
16. Race of mother black	42,906	22.3	4,217	30.1
17. Rural residence	67,069	34.9	5,346	38.2
18. Smoking from birth record	23,524	12.3	2,871	20.5
19. Smoking from Healthy Start	19,401	10.1	4,114	29.4
20. STDs, past or current	768	0.1	340	2.4
21. Stressful life	73,601	38.3	13,102	93.6

unadjusted odds ratios, upper and lower confidence intervals and p-values are summarized in Table 10 for LBW, Table 11 for TLBW and Table 12 for PTLBW.

Table 10. Unadjusted Odds Ratios for Low Birth Weight Based on Bi-variate Analysis of Independent Variables in the Study Sample.

Variable	OR	95% CI	p value
1. Age < 18, > 40	1.39	1.27, 1.54	0.0004
2. Alcohol use from birth record	0.18	0.11, 0.27	0.0000
3. Alcohol use from Healthy Start screen	1.35	1.23, 1.48	0.0016
4. Birth interval short	1.11	1.01, 1.21	0.2573
5. Chlamydia positive	1.88	1.28, 2.74	0.0012
6. High school - no	0.83	0.72, 0.97	0.0173
7. Gonorrhea positive	2.96	2.01, 4.36	0.0050
8. Inadequate PNC indices	1.42	1.32, 1.53	0.0000
9. Inadequate weight gain	3.12	2.90, 3.36	0.0000
10. Married – not	1.49	1.38, 1.61	0.0000
11. Medical history	1.35	1.21, 1.51	0.0058
12. Mistimed pregnancy	1.11	1.04, 1.20	0.1383
13. Mom foreign born	0.76	0.64, 0.91	0.0020
14. Mom LBW	1.66	1.50, 1.84	0.0000
15. Prior poor pregnancy outcome	1.95	1.80, 2.11	0.0000
16. Race of mother black	1.98	1.84, 2.13	0.0000
17. Rural residence	0.91	0.79, 1.05	0.2103
18. Smoking from birth record	1.57	1.45, 1.70	0.0000
19. Smoking from Healthy Start	1.28	1.18, 1.38	0.0012
20. STDs, past or current	2.04	1.71, 2.43	0.0001
21. Stressful life	0.89	0.74, 1.08	0.2348

A positive chlamydia test was found significantly associated with low birth weight (OR 1.88), term low birth weight (OR 1.87), and pre-term low birth weight (OR 1.86). In the pilot study on which this study was modeled, chlamydial infection was also significantly associated with low birth weight (OR 2.40), term low birth weight (OR 2.40), and pre-term low birth weight (OR 2.19) at the bivariate level of analysis. Two other STD related risks were examined, infection with gonorrhea and a pooled variable that included syphilis, infant infection, and maternal chlamydia and gonorrhea. The variable indicating

gonorrheal infection was significantly associated with low birth weight (OR 2.9) and term low birth weight (OR 4.2) dependent variables. Having a positive test result for gonorrhea increased the odds of low birth weight by nearly three times, and increased the likelihood of term low birth weight by more than fourfold. No association was observed for pre-term low birth weight events. Pooled STDs doubled the odds for all groups of low birth weight (OR 2.04, OR 2.08, and OR 1.90).

Several indicators were identified as mildly protective in reducing the odds of LBW. Significant variables included not being a high school graduate and if the mother was foreign born. Residing in a rural community and having a 'stressful' life were mildly protective, but not significant at 95% confidence interval, perhaps an artifact of the data or result of randomness. Alcohol use at any time during the pregnancy, information taken from the birth record, was significantly associated with low birth weight (p 0.0000 and OR 0.18). It is likely that this is an unreliable finding in light of the fact that only 1.1% of all women in the study sample admitted to alcohol use during pregnancy. Alternatively this discrepancy may be the result of a coding error. In comparison, 13.6% of women were identified as having used alcohol during the two months prior to completeing the Healthy Start prenatal screen (OR 1.69, $p < 0.0001$). Several other variables were found to only mildly increase the probability of a LBW event. Among these variables were: age under 18 or over 40 years, a mistimed pregnancy, a short birth interval, inadequate prenatal care indices, and a medical history. Inconsistency between odds ratios and LBW, TLBW and PTLBW were noted for the four alcohol and tobacco indicators. Increased odds were noted for unmarried women and those who themselves were of low birth weight.

The strongest indicator in all low birth weight events was an inadequate weight gain: OR of 3.12 for LBW, OR 2.56 for TLBW, and 3.35 with PTLBW. (Please refer to Tables 10 -12.) Examination of inadequate weight gain between women of different race/ethnicity groups indicates that both white and black women were 20% more likely to have inadequate weight gain with short inter pregnancy intervals. For both white and black

Table 11. Unadjusted Odds Ratios for Term Low Birth Weight, Based on Bi-variate Analysis of Independent Variables in the Study Sample.

Variable	OR	95% CI	p value
1. Age < 18, > 40	1.32	1.00, 1.75	0.0491
2. Alcohol use from birth record	4.17	2.42, 7.17	0.0000
3. Alcohol use from Healthy Start screen	1.69	1.31, 2.20	0.0001
4. Birth interval short	0.80	0.61, 1.06	0.1173
5. Chlamydia positive	1.87	1.06, 3.30	0.0305
6. High school - no-	0.94	0.75, 1.18	0.6023
7. Gonorrhea positive	4.23	1.67, 10.70	0.0024
8. Inadequate PNC indices	1.40	1.13, 1.74	0.0021
9. Inadequate weight gain	2.56	2.06, 3.17	0.0000
10. Married – not	1.38	1.10, 1.73	0.0048
11. Medical history	1.05	0.74, 1.49	0.7899
12. Mistimed pregnancy	1.19	0.96, 1.47	0.1121
13. Mom foreign born	0.75	0.57, 0.97	0.0298
14. Mom LBW	1.95	1.47, 2.58	0.0000
15. Prior poor pregnancy outcome	1.84	1.46, 2.31	0.0000
16. Race of mother black	1.70	1.38, 2.11	0.0000
17. Rural residence	0.93	0.75, 1.16	0.5399
18. Smoking from birth record	2.05	1.64, 2.56	0.0000
19. Smoking from Healthy Start	1.49	1.20, 1.85	0.0003
20. STDs, past or current	2.08	1.26, 3.42	0.0042
21. Stressful life	0.90	0.68, 1.18	0.4460

Table 12. Unadjusted Odds Ratios for Pre-Term Low Birth Weight, Based on Bi-variate Analysis of Independent Variables in the Study Sample.

Variable name	OR	95% CI	p value
1. Age < 18, > 40	1.43	1.13, 1.81	0.0032
2. Alcohol use from birth record	1.32	0.61, 2.82	1.5195
3. Alcohol use from Healthy Start screen	1.09	0.84, 1.41	0.5156
4. Birth interval short	1.23	0.98, 1.53	0.7690
5. Chlamydia positive	1.86	1.14, 3.02	0.0128
6. High school - no-	0.77	0.64, 0.94	0.0081
7. Gonorrhea positive	1.74	0.54, 5.59	0.3551
8. Inadequate PNC indices	1.41	1.17, 1.70	0.0003
9. Inadequate weight gain	3.35	2.79, 4.03	0.0000
10. Married – not	1.54	1.26, 1.88	0.0000
11. Medical history	1.57	1.21, 2.04	0.0008
12. Mistimed pregnancy	1.05	0.09, 1.26	0.5792
13. Mom foreign born	0.78	0.62, 0.98	0.0327
14. Mom LBW	1.41	1.08, 1.85	0.0126
15. Prior poor pregnancy outcome	1.95	1.60, 2.38	0.0000
16. Race of mother black	2.12	1.77, 2.55	0.0000
17. Rural residence	0.90	0.74, 1.09	0.2708
18. Smoking from birth record	1.22	0.98, 1.51	0.0657
19. Smoking from Healthy Start	1.11	0.92, 1.36	0.2810
20. STDs, past or current	1.90	1.21, 2.99	0.0052
21. Stressful life	0.90	0.71, 1.15	0.3989

women, twice as many women with inadequate weight gain experienced low birth weight events regardless of whether or not the inter pregnancy interval was short. Among women who stated that the pregnancy was mistimed, 30% more black women had inadequate weight gain. For women who stated that the timing of the pregnancy was acceptable, three times as many white women had inadequate weight gain (this data not shown).

Fetal deaths were not equally distributed across body mass index (BMI) groups; women of normal BMI accounted for 52.3% of the 88 fetal deaths. Both term and pre-term low birth weight percentages were highest in women of low BMI, 3.6% and 4.2%

respectively. Women 14 years and less had the highest rate of low birth weight at 10.1%, with women over 40 years of age second highest with a rate of 9.6%. The BMI group within these ages differed regarding which weight group had the highest proportion of the low birth weight. For the younger age group those with low BMI had the greatest percent of overall LBW (12.7%). In the older age group, more LBW occurred in women with high BMI (20.4%). Regardless of race/ethnicity group, the rate of low birth weight was highest in those groups of women with low body mass index.

Mothers of 1) black race, and 2) a prior poor pregnancy outcome were also significantly associated with all categories of low birth weight. Having had a STD in the past, or a positive test for chlamydia and gonorrhea were also significantly associated with all categories of low birth weight, especially gonorrhea infection.

Descriptive Analysis of 1996 Statewide Gen-Probe PACE2C® Results

The data set includes 128,786 laboratory reports of statewide specimens submitted to the State Bureau of Laboratories and tested by the Gen-Probe PACE2C® system for *Chlamydia trachomatis* and *Neisseria gonorrheae*. (Please refer to Table 13.) The distribution of test results for the time span utilized in accordance with the protocols for this data set, reveal that the majority of the specimens were collected in the second half of the time period. Sixty-three of the sixty-seven Florida counties are represented within the data set. However, the distribution reflects the phased in implementation of computerized storage of the laboratory records, and the failure of hardware as described in prior sections. Reports for forty counties individually represent less than 1% of the total test reports with test volumes ranging from 1 to 1,213 specimens. Twenty counties represent

from ≥1 to 5% of the total test reports with test volumes ranging from 1,311 to 5,944. Two counties are represented with volumes of >5 to 10% (5.6%, 6.9%) and two counties represent more than 10% each (11.2%, 12.4%) of the total test report database. Less than 1% of reports are associated with no identified county of specimen origin. The findings are presented in Table 13 below. No chlamydia related laboratory test results are available for the general population delivering during 1996.

Age is reported on nearly all records with only 0.6% identified as age unknown. The span of age groups between 15 and 34 years, represents 81.8% of the test reports. Gender is identified on 99% of reports. Program code is identified on 77.4% of the specimen reports with 11.3% identified as collected from women who received prenatal care services. Of the five branch laboratory sites, Jacksonville is over represented, contributing 63% of the specimen reports, and Pensacola is second with 12.9%. Race/ethnicity is identified on all but 3.3% of the reports.

The highest positivity for chlamydia is among those under twenty years of age, with 15 to 19 year olds reported at 9.3% and <15 years at 9.6%. Those women identified as being of black race/ethnicity have greater than twice the positivity of whites in this database (7.5% and 3.0% respectively) with males nearly twice the rate of females (7.3% and 4.2% respectively). The positivity at 5.5% for chlamydia specimens collected from prenatal clinics is greater than that of all other program areas except for STD clinic settings. In contrast, the highest positivity for gonorrhea specimens is 11.1% from STD clinics, followed by 6.7% from unknown clinic settings. The rate of dual infection with

Table 13. 1996 Statewide Chlamydia and Gonorrhea Prevalence Estimates Based on Laboratory Test Results.

		Chlamydia +		Gonorrhea +		Dual Infected	
	# of records	%	#	%	#	%	#
Total	128,786	4.7	6,106	4.4	5,690	0.6	795
Age Category							
< 15 years	1,261	9.6	121	4.2	53	1.6	20
15 – 19 years	27,219	9.3	2,530	5.3	1,430	1.4	382
20 - 24 years	35,490	6.1	2,176	4.7	1,689	0.7	254
25 – 29 years	23,973	3.0	735	3.7	893	0.3	76
30 –34 years	16,834	1.8	296	3.6	613	0.2	33
35 – 39 years	11,226	1.1	127	4.1	465	0.1	15
40 – 44 years	5,895	0.7	43	4.7	274	0.1	5
> 45 years	6,119	0.6	39	3.8	234	0.1	7
Race/ethnicity							
Black	48,748	7.5	3,666	9.6	4,436	1.3	637
Hispanic	1,920	4.6	92	2.4	46	0.2	4
Other	1,293	4.2	54	2.3	20	0.3	46
White	72,605	3.0	2,139	1.2	859	0.2	141
Unknown	1,917	4.3	81	1.8	33	0.2	3
Gender							
Female	107,222	4.2	4.2	1.8	1,928	0.5	553
Male	21,615	7.3	7.3	17.3	4,849	1.1	236
Unknown	1,917	5.1	5.1	2.5	4	-	-
Program code							
Family Planning	52,096	3.6	1,852	0.9	462	0.3	158
HIV Clinic	189	1.1	2	4.8	9	-	-
Other	6,819	2.2	150	1.4	96	0.2	16
Pre Natal	14,655	5.5	796	1.1	153	0.5	72
STD Clinic	28,966	6.5	1,856	11.1	3,169	1.1	312
Unknown	27,126	5.4	1,450	6.7	1,801	0.9	237

Content adapted from: Schmitt, 1996a.

both chlamydia and gonorrhea was highest in those younger than 19 years. Among the 15 to 19 year olds, the rate was 1.4%, and 1.6% for those younger than 15 years.

Of the 14,655 records identified as from specimens collected in prenatal clinics, 92.9% span the ages from 15 to 34 years. The highest chlamydial positivity is among those 15 to 19 years of age (9.8%). Among the 88 pregnant adolescents under 15 years, 12 were reported as positive (13.6%). While a higher positivity than the next age group, the sample is smaller and the difference was not significant. The highest gonorrhea positivity among pregnant females 93.4%) is also from this youngest age group. The overall positivity for all persons tested is similar for chlamydia and gonorrhea at 4.7% and 4.4% respectively. For pregnant women, the overall positivity for chlamydia is 5.5%, for gonorrhea, 1.1%, and 0.5% were infected with both. From this data set, 8,334 test results were linked to a birth or fetal death record.

Logistic Regression Results

The study sample database was initially examined through four sets of logistic regression models. Following application of the four models and interpretation of the findings, two more models were fitted to the sample population. The odds ratios for each predictive variable and the outcomes from the fifth and sixth models are presented following the discussion on the initial four models (please refer back to Figure 4.). The first model examined the entire sample and included a race indicator. This was subsequently repeated in the second model without the race indicator. The third model analyzed only data pertaining to women of white race. The fourth model examined women of black race. Each of these four models was broken into three sub-samples to better

understand potential differences in observed associations from the bi-variate analysis. These three breakouts were: 1) women with a low birth weight infant, 2) women with a term low birth weight infant, and 3) women with pre-term low birth weight infant. All models excluded women with multiple gestation and delivered by Cesarean section. The results identified very distinct differences between the independent variables and the dependent variables of LBW, TLBW, and PTLBW. All variables in each of the four sets of models were entered into backwards elimination (logistic regression) in the same order. They were removed in each run at different steps and in differing order of significance relative to the sub-samples. A summary follows of the more notable differences observed related to sexually transmitted infections and the overall most significant associations identified for increased risk of low birth weight. Nearly all models identified "inadequate weight gain" as the most significantly associated independent variable contributing to any event of low birth weight. The first set was run with a race indicator entered among the independent variables, coded '0' for white race and '1' for black race. Tables 14 to 17 present the data at the final step in each logistic model for this set. Where applicable, STD related indicators are bolded for easier recognition.

Logistic Model One: All CHD with race indicator – low birth weight. The first set included all women and a race indicator. The first sub-sample model in this set examined women identified as having a low birth weight infant. Due to missing data on 161 of the 14,002 women in the study sample, 13,841 cases were included in this analysis of ten steps. (Please refer to Table 14.) The chlamydial infection indicator was eliminated at the 2nd step (OR 1.23, p-value .8125, 95% CI .4040, 3.1771). The gonorrheal infection indicator was eliminated at the 7th step (OR 1.29, p-value .5718, 95% CI .5347, 3.1075).

Table 14. Adjusted Odds Ratios, Based on Logistic Regression, for all Variables.

Low Birth Weight

Variable	OR	95% CI	p value
High school graduate - not	0.83	0.69, 1.00	0.0489
Inadequate weight gain	2.52	2.19, 2.91	0.0000
Married – not	1.21	1.03, 1.42	0.0177
Mom LBW	1.49	1.22, 1.82	0.0001
Prior poor pregnancy outcome	1.81	1.55, 2.12	0.0000
Race of mother black	1.89	1.62, 2.20	0.0000
Smoking from birth record	1.74	1.47, 2.07	0.0000
STDs, past or current	**1.48**	**1.04, 2.11**	**0.0278**

Term Low Birth Weight

Variable	OR	95% CI	p value
Age < 18, > 40	1.49	0.11, 1.99	0.0080
Alcohol use from Healthy Start screen	1.43	1.07, 1.90	0.0157
Birth interval short	0.73	0.55, 0.99	0.0400
Inadequate PNC indices	1.31	1.05, 1.63	0.0176
Inadequate weight gain	2.46	1.97, 3.07	0.0000
Mom LBW	1.86	1.40, 2.43	0.0000
Prior poor pregnancy outcome	1.86	1.46, 2.39	0.0000
Race of mother black	1.86	1.47, 2.34	0.0000
Smoking from birth record	2.17	1.69, 2.80	0.0000
STDs, past or current	**1.79**	**1.07, 3.00**	**0.0269**

Pre-Term Low Birth Weight

Variable	OR	95% CI	p value
High school graduate - not	0.68	0.56, 0.84	0.0002
Inadequate PNC indices	1.26	1.04, 1.53	0.0171
Inadequate weight gain	3.31	2.74, 4.00	0.0000
Married – not	1.24	1.00, 1.54	0.0468
Medical history	1.44	1.10, 1.89	0.0081
Mom LBW	1.36	1.03, 1.79	0.0308
Prior poor pregnancy outcome	1.91	1.55, 2.34	0.0000
Race of mother black	2.03	1.65, 2.50	0.0000
Smoking from Healthy Start screen	1.45	1.17, 1.80	0.0007

Pregnant women in the low birth weight sub-sample exhibited a substantially higher risk for low birth weight associated with the following independent variables:

OR 2.52, mother had inadequate weight gain

OR 1.88, mother was of black race

OR 1.80, a history of a prior poor pregnancy outcome

OR 1.74, identified as having smoked at any time during pregnancy

OR 1.49, mother weighed less than 5.5 pounds when she was born

OR 1.48, a history of any sexually transmitted infections

OR 1.21, mother not married

Logistic Model One: All CHD with race indicator – TLBW. The second sub-sample model in this set examined women identified as having a low birth weight infant. Due to missing data on 613 of the 14,002 women in the study sample, 13,389 cases were included in this analysis of ten steps. Please refer to Table 14.

The chlamydial infection indicator was eliminated at the 2nd step due to low significance. The gonorrheal infection indicator was retained until the final step (OR 2.16, p-value .1843, 95% CI .6929, 6.7371). Pregnant women in this sub-sample exhibited a substantially higher risk for TLBW associated with the following independent variables:

OR 2.46, mother had inadequate weight gain

OR 1.78, identified as having smoked at any time during pregnancy

OR 1.86, mother weighed less than 5.5 pounds when she was born

OR 1.86, a history of a prior poor pregnancy outcome

OR 1.85, mother was of black race

OR 1.79, a history of any sexually transmitted infections

OR 1.48, age under18 or over 40 years

OR 1.43, use drugs or alcohol in the two months prior to HS Screen

OR 1.31, indices of inadequate prenatal care visits

Counter intuitively, women in this set also were 27% less likely to experience a TLBW infant if the interval from their previous pregnancy was less than nine months.

Logistic Model One: All CHD with race indicator – PTLBW. The third sub-sample model in this set examined women identified as having a pre-term low birth weight infant. Due to missing data on 493 of the 14,002 women in the study sample, 13,509 cases were included in this analysis and terminated after the 13th step. (Please refer to Table 14.)

The gonorrheal infection and any sexually transmitted infection indicators were eliminated at the 4th and final 5th steps due to low significance. The chlamydial infection indicator was retained until the final step (OR 1.48, p-value .1252, 95% CI .6859, 2.4590). Pregnant women in this sub-sample exhibited a substantially higher risk for PTLBW associated with the following independent variables:

OR 3.31, mother had inadequate weight gain

OR 2.03, mother was of black race

OR 1.91, a history of a prior poor pregnancy outcome

OR 1.45, use of any form of tobacco in the two months prior to HS Screen

OR 1.44, a history of medical conditions during pregnancy

OR 1.79, mother weighed less than 5.5 pounds when she was born

OR 1.26, indices of inadequate prenatal care visits

OR 1.24, mother not married mother not married

Again, surprisingly, women in this set also were 32% less likely to experience a PTLBW infant if the mother was not a high school graduate. The second set was run without any identification of race entered among the independent variables. Table 15 presents the data at the final step in each logistic model for this set.

Logistic model two: All CHD without any race indicator – low birth weight. As in the first set of models, the first sub-sample examined women identified as having a low birth weight infant. Due to missing data on 161 of the 14,002 women in the study sample, 13,841 cases were included in this analysis and terminated after the 11th step. (Please refer to Table 15.)

The chlamydial infection indicator was eliminated at the 2nd step due to low significance. The gonorrheal infection indicator was eliminated at the 5th step (OR 1.41, p-value .4366, 95% CI .5907, 3.3848). Pregnant women in the low birth weight 'non-race' sub-sample exhibited a substantially higher risk for low birth weight associated with the following independent variables:

OR 2.63, mother had inadequate weight gain

OR 1.88, use of alcohol at any time during pregnancy

OR 1.88, a history of a prior poor pregnancy outcome

OR 1.70, a history of any sexually transmitted infections

OR 1.53, mother weighed less than 5.5 pounds when she was born

OR 1.48, identified as having smoked at any time during pregnancy

OR 1.46, mother not married

Table 15. Adjusted Odds Ratios, Based on Logistic Regression, without Race Variable.

Low Birth Weight

Variable	OR	95% CI	p value
Alcohol use from birth record	2.02	1.29, 3.16	0.0022
High school graduate - not	0.82	0.68, 1.00	0.0438
Inadequate weight gain	2.63	2.29, 3.03	0.0000
Married – not	1.45	1.25, 1.69	0.0000
Mom LBW	1.53	1.26, 1.87	0.0000
Prior poor pregnancy outcome	1.87	1.61, 2.19	0.0000
Smoking from birth record	1.48	1.27, 1.74	0.0000
STDs, past or current	**1.70**	**1.20, 2.41**	**0.0029**

Term Low Birth Weight

Variable	OR	95% CI	p value
Age < 18, > 40	1.50	1.12, 2.02	0.0066
Alcohol use from birth record	2.23	1.23, 4.05	0.0086
Alcohol use from Healthy Start screen	1.38	1.04, 1.84	0.0276
Birth interval short	0.73	0.55, 0.99	0.0411
Inadequate PNC indices	1.30	1.05, 1.63	0.0185
Inadequate weight gain	2.58	2.07, 3.21	0.0000
Married – not	1.27	1.01, 1.61	0.0456
Mom LBW	1.91	1.44, 2.55	0.0000
Prior poor pregnancy outcome	1.93	1.51, 2.47	0.0000
Smoking from birth record	1.83	1.44, 2.33	0.0000
STDs, past or current	**2.01**	**1.21, 3.36**	**0.0075**

Pre-Term Low Birth Weight

Variable	OR	95% CI	p value
High school graduate - not	0.68	0.55, 0.82	0.0001
Inadequate PNC indices	1.26	1.04, 1.53	0.0181
Inadequate weight gain	3.40	2.82, 4.11	0.0000
Married – not	1.52	1.24, 1.86	0.0001
Medical history	1.42	1.09, 1.87	0.0105
Mom LBW	1.40	1.06, 1.84	0.0181
Prior poor pregnancy outcome	1.97	1.60, 2.41	0.0000
STDs, past or current	**1.65**	**1.03, 2.62**	**0.0362**

Logistic model two: All CHD without any race indicator – TLBW. The second sub-sample model in this set examined women identified as having a low birth weight infant. Due to missing data on 613 of the 14,002 women in the study sample, 13,389 cases were included in this analysis and terminated after the 10th step. (Please refer to Table 15.).

The chlamydial infection indicator was eliminated at the 3rd step due to low significance. The gonorrheal infection indicator was retained until the 9th step (OR 2.36, p-value .1367, 95% CI .7616, 7.3117). Pregnant women in this sub-sample exhibited a substantially higher risk for TLBW associated with the following independent variables:

OR 2.58, mother had inadequate weight gain

OR 2.23, use of alcohol at any time during pregnancy

OR 2.01, a history of any sexually transmitted infections

OR 1.93, a history of a prior poor pregnancy outcome

OR 1.91, mother weighed less than 5.5 pounds when she was born

OR 1.83, identified as having smoked at any time during pregnancy

OR 1.50, age under18 or over 40 years

OR 1.38, use drugs or alcohol in the two months prior to HS Screen

OR 1.30, indices of inadequate prenatal care visits

OR 1.27, mother not married

As with the first model for TLBW, women in this set also were 27% less likely to experience a TLBW infant if the interval from their previous pregnancy was less than nine months from the their last menstrual period before this pregnancy.

Logistic model two: All CHD without any race indicator – PTLBW. The third sub-sample model in this set examined women identified as having a pre-term low birth weight infant. Due to missing data on 493 of the 14,002 women in the study sample, 13,509 cases were included in this analysis and terminated after the 12th step. (Refer to Table 15.).

The gonorrheal infection indicator was eliminated at the 2nd due to low significance. The chlamydial infection indicator was retained until the 5th step (OR 1.20, p-value .7937, 95% CI .3240, 4.3674). Pregnant women in this sub-sample exhibited a substantially higher risk for PTLBW associated with the following independent variables:

OR 3.40, mother had inadequate weight gain

OR 1.97, a history of a prior poor pregnancy outcome

OR 1.65, a history of any sexually transmitted infections

OR 1.52, mother not married

OR 1.42, a history of medical conditions during pregnancy

OR 1.40, mother weighed less than 5.5 pounds when she was born

OR 1.26, indices of inadequate prenatal care visits

Again, surprisingly, women in this set also were 32% less likely to experience a PTLBW infant if the mother was not a high school graduate.

Logistic model three: Women of white race only – low birth weight. The third set included only women of white race. Due to missing data on 91 of the 9,492 white women in the study sample, 9,401 cases were included in this analysis and terminated after the 12th step. (Please refer to Table 16.)

With the decreasing sample, all STD related indicators were eliminated at the 7th to 9th step with high odds ratios and excessively wide confidence intervals bridging 1.0. This

Table 16. Adjusted Odds Ratios, Based on Logistic Regression, for White Race.

Low Birth Weight			
Variable	**OR**	**95% CI**	**p value**
Inadequate weight gain	2.65	2.19, 3.21	0.0000
Married – not	1.28	1.06, 1.55	0.0108
Medical history	1.38	1.06, 1.81	0.0176
Mom foreign born	1.28	1.02, 1.61	0.0364
Mom LBW	1.38	1.04, 1.83	0.0259
Prior poor pregnancy outcome	1.56	1.26, 1.94	0.0000
Smoking from birth record	1.87	1.52, 2.31	0.0000
Term Low Birth Weight			
Variable	**OR**	**95% CI**	**p value**
Alcohol use from Healthy Start screen	1.59	1.13, 2.24	0.0078
Inadequate weight gain	2.45	1.82, 3.31	0.0000
Mom LBW	1.53	1.01, 2.30	0.0434
Prior poor pregnancy outcome	1.59	1.15, 2.18	0.0045
Smoking from birth record	2.17	1.61, 2.92	0.0000
Pre-Term Low Birth Weight			
Variable	**OR**	**95% CI**	**p value**
Inadequate weight gain	3.75	2.89, 4.87	0.0000
Married – not	1.38	1.06, 1.80	0.0161
Medical history	1.73	1.21, 2.46	0.0024
Mom foreign born	1.44	1.05, 1.98	0.0255
Prior poor pregnancy outcome	1.43	1.06, 1.93	0.0178
Smoking from Healthy Start screen	1.68	1.25, 2.23	0.0006

reflects the inadequate power in this variable, with insufficient positive test results to accurately predict associations. The following independent variables were associated with an increased risk of low birth weight among white women:

OR 2.65, mother had inadequate weight gain

OR 1.87, identified as having smoked at any time during pregnancy

OR 1.56, a history of a prior poor pregnancy outcome

OR 1.38, a history of medical conditions during pregnancy

OR 1.28, mother not married

OR 1.28, mother born in another country

OR 1.38, mother weighed less than 5.5 pounds when she was born

Logistic model three: Women of white race only – TLBW. Due to missing data on 320 of the 9,492 white women in the study sample, 9,172 cases were included in this analysis and terminated after the 15th step. (Please refer to Table 16.).

As in the first sub-sample, all STD related indicators were eliminated only a bit later at the 10th to 12th step with high odds ratios and excessively wide confidence intervals bridging 1.0, reflecting the inadequate power in this variable. Unlike the larger sized sub-samples, fewer variables remained in the final model.

OR 2.45, mother had inadequate weight gain

OR 2.17, identified as having smoked at any time during pregnancy

OR 1.59, use drugs or alcohol in the two months prior to HS Screen

OR 1.59, a history of a prior poor pregnancy outcome

OR 1.53, mother weighed less than 5.5 pounds when she was born

Logistic model three: Women of white race only – PTLBW. The third sub-sample model in this set examined women identified as having a pre-term low birth weight infant. Due to missing data on 493 of the 14,002 women in the study sample, 13,509 cases were included in this analysis of 13 steps. (Please refer to Table 16.).

The gonorrheal infection and any sexually transmitted infection indicators were eliminated at the 4th and final 5th steps due to low significance. The chlamydial infection indicator was retained until the final step (OR 1.48, p-value .1252, 95% CI .6859, 2.4590). Pregnant women in this sub-sample exhibited a substantially higher risk for PTLBW associated with the following independent variables:

OR 3.75, mother had inadequate weight gain

OR 1.73, a history of medical conditions during pregnancy

OR 1.67, use any form of tobacco in the two months prior to HS Screen

OR 1.44, mother born in another country

OR 1.43, a history of a prior poor pregnancy outcome

OR 1.39, mother not married

Logistic model four: Women of black race only – low birth weight. The final set included only women of black race. Due to missing data on 68 of the 4,217 black women in the study sample, 4,149 cases were included in this analysis and terminated after the 14th step. (Please refer to Table 17.)

The gonorrheal and chlamydial infection indicators were eliminated at the 5th and 7th steps due to low significance. The independent variables found strongly associated with an increased risk of low birth weight were fewer and two were identified as protective:

OR 2.67, mother had inadequate weight gain

OR 2.67, a history of a prior poor pregnancy outcome

OR 1.93, identified as having smoked at any time during pregnancy

OR 1.78, a history of any sexually transmitted infections

OR 1.58, mother weighed less than 5.5 pounds when she was born

OR 0.62, mother born in another country

OR 0.58, mother not a high school graduate

Table 17. Adjusted Odds Ratios, Based on Logistic Regression, for Black Race.

Low Birth Weight

Variable	OR	95% CI	p value
High school graduate - not	0.58	0.46, 0.72	0.0000
Inadequate weight gain	2.27	1.83, 2.82	0.0000
Mom foreign born	0.63	0.44, 0.88	0.0073
Mom LBW	1.58	1.18, 1.12	0.0023
Prior poor pregnancy outcome	2.27	1.80, 2.86	0.0000
Smoking from birth record	1.93	1.40, 2.67	0.0001
STDs, past or current	**1.78**	**1.20, 2.65**	**0.0046**

Term Low Birth Weight

Variable	OR	95% CI	p value
Alcohol use from birth record	2.39	1.04, 5.49	0.0396
High school graduate - not	0.57	0.40, 0.81	0.0016
Inadequate weight gain	2.46	1.75, 3.45	0.0000
Mom LBW	2.18	1.43, 3.34	0.0003
Prior poor pregnancy outcome	2.09	1.45, 3.01	0.0001
Smoking from birth record	2.43	1.48, 4.01	0.0005
STDs, past or current	**2.24**	**1.24, 4.04**	**0.0073**

Pre-Term Low Birth Weight

Variable	OR	95% CI	p value
High school graduate - not	0.58	0.43, 0.77	0.0002
Inadequate weight gain	2.78	2.10, 3.68	0.0000
Mom foreign born	0.50	0.31, 0.81	0.0044
Prior poor pregnancy outcome	2.60	1.93, 3.49	0.0000
STDs, past or current	**1.72**	**1.03, 2.86**	**0.0383**

Logistic model four: Women of black race only – TLBW. Due to missing data on 284 of the 4,217 women in the study sample, 3,933 cases were included in this analysis and terminated after the 13th step. The gonorrheal and chlamydial infection indicators were eliminated at the 7th and 9th steps due to low significance. Overall most variables had a higher odds ratio than in other sub-samples. Again mother not being a high school graduate decreased her risk of experiencing a PTLBW event by 43%. (Please refer to Table 17.)

OR 2.46, mother had inadequate weight gain

OR 2.43, identified as having smoked at any time during pregnancy

OR 2.39, use of alcohol at any time during pregnancy

OR 2.24, a history of any sexually transmitted infections

OR 2.18, mother weighed less than 5.5 pounds when she was born

OR 2.10, a history of a prior poor pregnancy outcome

OR 0.57, mother not a high school graduate

Logistic model four: Women of black race only – PTLBW. Due to missing data on 210 of the 4,217 black women in the study sample, 4,007 cases were included in this analysis. The analysis was terminated after the 15th step. The gonorrheal and chlamydial infection indicators were eliminated at the 4th and 9th steps due to low significance. As in the other models for this sub-sample, a history of any sexually transmitted infection remained significantly associated with an increased risk of PTLBW. Two variables were again protective: lack of a high school diploma and mother born outside of this country. (Please refer to Table 17.)

OR 2.65, mother had inadequate weight gain

OR 1.78, a history of a prior poor pregnancy outcome

OR 1.86, a history of any sexually transmitted infections

OR 0.58, mother not a high school graduate

OR 0.50, mother born in another country

Summary of adjusted odds ratios from initial four logistic models. Review of these initial four sets of models suggests that the associations found may be strongly tempered by numerous factors independent of race and gestation. For example, while the fact of a women having been born in another country increased the risk of a LBW event for white women, it was protective at a similar level for black women (> 44% versus < 37% respectively). In all models, inadequate weight gain during pregnancy was the most significant risk. Sexually transmitted infections appear to have a more significant association with PTLBW and disproportionately so among minority women. However, sexually transmitted infections were associated with all levels of low birth weight across the various models. The lack of a high school diploma increased the risk of LBW among women of white race, but not for women of black race. Overall, very unexpected associations were identified for the sample in general and for the sub-samples.

The overwhelming influence of inadequate weight gain as a predictor of low birth weight outcomes suggested that examination of the sample variables, while controlling for the weight gain, might provide other information and affect the odds ratios for the other independent predictor variables included in the model. Among all women in the study sample, 22% were identified as not gaining adequate weight during their pregnancy. Two more models were applied to control for inadequate weight gain. As with the initial four

models, logistic regression run was broken into three sub-samples to address the dependent variables of LBW, TLBW, and PTLBW. Again all models excluded women with multiple gestation and delivered by Cesarean section. All variables in the fifth model were again entered into backwards elimination (LR) in the same order. The results of these final models identified a totally different grouping of associations between the independent variables and the dependent variables, once inadequate weight gain was controlled for in the models.

Logistic Model Five: All CHD with race indicator and inadequate weight gain – low birth weight. The fifth model examined women identified with inadequate weight gain, controlling for those who did gain the recommended amount for their body mass index and length of gestation. The low birth weights analysis terminated after the 15th step and included 3,079 excluding the 21 for missing data. (Please refer to Table 18.)

Prior infection with chlamydia was significantly associated with women who had not gained adequate weight during pregnancy and delivered a low birth weight infant. The gonorrheal indicator was eliminated at the 4th step and the STD indicator at the 5th step due to low significance with OR .9535, p-value .9416, 95% CI .2671, 3.4039 and OR 2.33, p-value .0827, 95% CI .8963, 6.0566, respectively. In addition to the chlamydial indicator pregnant women in the low birth weight inadequate weight gain sub-sample exhibited a substantially higher risk for low birth weight associated with the following independent variables:

OR 2.36, use of alcohol at any time during pregnancy

OR 2.08, mother weighed less than 5.5 pounds when she was born

OR 1.99, a history of chlamydial infection in pregnancy

Table 18. Adjusted Odds Ratios, Based on Logistic Regression, for Inadequate Weight Gain.

Low Birth Weight

Variable	OR	95% CI	p value
Alcohol use from birth record	2.36	1.19, 4.72	0.0146
Chlamydia positive	**1.98**	**1.12, 3.51**	**0.0184**
High school graduate - not	0.66	0.52, 0.84	0.0008
Married – not	1.37	1.06, 1.78	0.0182
Mom LBW	2.07	1.54, 2.79	0.0000
Prior poor pregnancy outcome	1.96	1.53, 2.50	0.0000
Race of mother black	1.51	1.17, 1.95	0.0014
Smoking from Healthy Start screen	1.76	1.37, 2.27	0.0000

Term Low Birth Weight

Variable	OR	95% CI	p value
Alcohol use from birth record	3.62	1.57, 8.38	0.0026
High school graduate - not	0.63	0.43, 0.92	0.0178
Medical history	0.48	0.24, 0.97	0.0412
Mistimed pregnancy	1.75	1.21, 2.54	0.0029
Mom LBW	2.93	1.94, 4.40	0.0000
Prior poor pregnancy outcome	2.19	1.51, 3.19	0.0000
Race of mother black	1.61	1.11, 2.33	0.0119
Smoking from birth record	2.35	1.58, 3.51	0.0000

Pre-Term Low Birth Weight

Variable	OR	95% CI	p value
Chlamydia positive	**2.34**	**1.23, 4.48**	**0.0099**
High school graduate - not	0.64	0.48, 0.87	0.0040
Married – not	1.61	1.16, 2.24	0.0046
Prior poor pregnancy outcome	1.90	1.40, 2.57	0.0000
Race of mother black	1.58	1.16, 2.15	0.0037
Smoking from Healthy Start screen	1.67	1.22, 2.29	0.0014

OR 1.96, a history of a prior poor pregnancy

OR 1.76, use of any form of tobacco in the two months prior to HS screen

OR 1.51, mother was of black race

OR 1.37, mother not married

Logistic Model Five: All CHD with race indicator and inadequate weight gain – term low birth weight. This sub-sample examined women identified with inadequate weight gain, controlling for those who did gain the recommended amount for their body mass index and length of gestation and who delivered a term low birth weight infant. The analysis terminated after the 13th step and included 2,864 excluding the 236 for missing data. (Please refer to Table 18.)

No STD related predictor variable was significantly associated with term low birth weight. The chlamydial indicator was removed at the 3rd step; the gonorrheal indicator was eliminated at the 6th step and the STD indicator at the 12th step. The following independent variables were identified as significant:

OR 3.62, use of alcohol at any time during pregnancy

OR 2.93, mother weighed less than 5.5 pounds when she was born

OR 2.35, identified as having smoked at any time during pregnancy

OR 2.19, a history of a prior poor pregnancy

OR 1.75, pregnancy was mistimed

OR 1.61, mother was of black race

Not having completed high school and a history of a medical condition during the pregnancy both reduced the likelihood of a term low birth weight event by 40% and 50% respectively.

Logistic Model Five: All CHD with race indicator and inadequate weight gain – pre-term low birth weight. The final sub-sample examined women identified with inadequate weight gain, controlling for those who did gain the recommended amount for their body mass index and length of gestation, and who delivered a pre-term infant. The analysis terminated after the 13th step and included 2,945 excluding the 155 for missing data. (Please refer to Table 18.)

Prior infection with chlamydia was significantly associated with women who had not gained adequate weight during pregnancy and delivered a pre-term low birth weight infant. The gonorrheal indicator was eliminated at the 7th step and the STD indicator at the 8th step due to low significance with OR .7199, p-value .7522, 95% CI .0936, 5.5352 and OR 1.24, p-value .7902, 95% CI .2560, 5.9939 respectively. The following independent variables were significant:

OR 2.34, a history of chlamydial infection in pregnancy

OR 1.90, a history of a prior poor pregnancy

OR 1.67, use of any form of tobacco in the two months prior to HS screen

OR 1.61, mother not married

OR 1.58, mother was of black race

Logistic Model Six: All CHD with race indicator and adequate weight gain – low birth weight. This final model (and first sub-sample) examined women identified with adequate weight gain, controlling for those who did not gain the recommended amount for their body mass index and length of gestation included 10,902, excluding the 140 for missing data. This analysis terminated after the 15th step. (Please refer to Table 19).

The chlamydial infection indicator was eliminated at the 2nd step due to low significance (OR .9535, p-value .9416, 95% CI .2671, 3.4039) and the gonorrheal infection indicator was eliminated at the 15th step (OR 2.33, p-value .0827, 95% CI .8963, 6.0566). Pregnant women in the low birth weight adequate weight gain sub-sample exhibited a substantially higher risk for low birth weight associated with the following independent variables:

OR 2.33, mother was of black race

OR 1.87, identified as having smoked at any time during

OR 1.71, a history of a prior poor pregnancy outcome

OR 1.43, age less than 18 years or more than 40 years

OR 1.32, a history of medical conditions during pregnancy

In this model women reporting a mistimed pregnancy were 20% less likely to experience a low birth weight event.

Logistic Model Six: All CHD with race indicator and adequate weight gain – term low birth weight. Due to missing data 377 cases were rejected and 10,525 remained in this sub-sample analysis that is terminated after the 13th step. The chlamydial infection indicator was eliminated at the 3rd step and the overall STD indicator at the 10th step. Of interest is that gonorrheal infection was identified as significantly associated with term low birth weight, however, with a rather wide confidence interval. (Please refer to Table 19.)

OR 2.33, a history of gonorrheal infection

OR 2.19, identified as having smoked at any time during pregnancy

OR 2.07, mother was of black race

OR 1.63, used drugs or alcohol in the last two prior to HS screen

OR 1.59, a history of a prior poor pregnancy outcome

OR 1.48, age less than 18 years or more than 40 years

OR 1.43, indices of inadequate prenatal care visits during pregnancy

Table 19. Adjusted Odds Ratios, Based on Logistic Regression, for Adequate Weight Gain.

Low Birth Weight

Variable	OR	95% CI	p value
Age < 18, > 40	1.43	1.12, 1.81	0.0035
Mistimed pregnancy	0.80	0.67, 0.96	0.0161
Medical history	1.32	1.02, 1.72	0.0349
Prior poor pregnancy outcome	1.71	1.41, 2.09	0.0000
Race of mother black	2.33	1.93, 2.81	0.0000
Smoking from birth record	1.87	1.52, 2.30	0.0000

Term Low Birth Weight

Variable	OR	95% CI	p value
Age < 18, > 40	1.48	1.01, 2.16	0.0437
Alcohol use from Healthy Start screen	1.63	1.15, 2.30	0.0062
Gonorrhea positive	**5.11**	**1.77, 14.75**	**0.0025**
Inadequate PNC indices	1.43	1.08, 1.90	0.0115
Prior poor pregnancy outcome	1.59	1.16, 2.18	0.0037
Race of mother black	2.07	1.53, 2.80	0.0000
Smoking from birth record	2.19	1.59, 3.01	0.0000

Pre-Term Low Birth Weight

Variable	OR	95% CI	p value
Age < 18, > 40	1.48	1.06, 2.07	0.0204
Inadequate PNC indices	1.34	1.04, 1.73	0.0252
Prior poor pregnancy outcome	1.88	1.42, 2.49	0.0000
Race of mother black	2.43	1.86, 3.17	0.0000
Smoking from birth record	1.48	1.07, 2.03	0.0163

Logistic Model Six: All CHD with race indicator and adequate weight gain – pre-term low birth weight. The pre-term sub-sample included 10,564 and excluded 338 cases. The analysis terminated after the 15th step. The chlamydial infection indicator was eliminated at the 2nd step, the gonorrheal indicator at the 4th step and the overall STD indicator at the 6th step. The following five variables remained significantly associated with pre-term low birth weight: (Please refer to Table 19.)

OR 2.45, mother was of black race a history of gonorrheal infection

OR 1.88, a history of a prior poor pregnancy

OR 1.48, age less than 18 years or more than 40 years

OR 1.63, used drugs or alcohol in the last two prior to HS screen

OR 1.48, identified as having smoked at any time during pregnancy

OR 1.34, indices of inadequate prenatal care visits during pregnancy

Summary of adjusted odds ratios from models five and six. In conclusion, the powerful influence of inadequate weight gain as a predictor of low birth weight events masked the significance of other variables identified in previous studies e.g., marital status, tobacco and alcohol use, and young and old age. Application of the final two models assisted in identification of this phenomenon. Additionally, in controlling for the effects of inadequate weight gain, a different association was noted between grouped STDs and chlamydia and gonorrhea individually with low birth weight. Insight was also gained into the contradictory findings between numerous studies that did not include the full spectrum of potential indicator variables as have been included in these analyses.

Other Related Study Findings of Interest

Insufficient literature has been published on the associations between sexually transmitted infections, low birth weight and other adverse pregnancy outcomes. No study published has controlled for each sexually transmitted infection, along with the many risks known to be significantly associated with low birth weight, and other adverse pregnancy outcomes, and also used highly sensitive laboratory tests prospectively in a controlled study to specifically examine the associations. This study was not explicitly designed to look at the role of other STDs and pregnancy outcomes. However, some data and their descriptive analysis within the context of this study merit further discussion.

Within the larger relational database, 427 case infant and maternal morbidity files were linked to birth and fetal death records. Additionally, other cases of sexually transmitted diseases were identified from the maternal and infant laboratory test records. Among those infected with either chlamydia or gonorrhea, no fetal death records were linked. Nine maternal morbidity cases were linked to fetal death records, all of which were of normal birth weight. Linkages between the laboratory tests included 437 chlamydia cases and 103 gonorrhea cases with live birth records. Very few of the women with positive laboratory tests were matched with the same infant who had a positive laboratory test linked to their record. Of the 67 linked congenital syphilis cases, 14 were either term or pre-term low birth weight (20.8%). Only 40 of the 67 congenital cases were matched to mothers identified as having a diagnosis of syphilis within the context of the relational database, 39% of which were to latent syphilis cases.

Among the study sample, all but two of the 35 matched maternal syphilis cases were reported as latent syphilis. This grouping included those with early latent syphlis and

late latent. A diagnosis of early latent syphilis is based on or more of the following criteria: 1) documented seroconversion or fourfold or greater increase in titer of a nontreponemal test during the previous 12 months; 2) a history of symptoms consistent with primary or secondary syphilis during the previous 12 months; 3) history of sexual exposure to a confirmed or probable primary or secondary case; and 4) reactive nontreponemal test and treponemal tests from a person whose only possible exposure occurred within the preceding 12 months (CDC, 1997b). While the numbers of linked STD cases in the study file are much fewer than those in the larger relational database, and it is of limited value to conclude anything from the results, the trends are the same. These include: 1) not all congenital syphilis cases were linked with a woman also identified as having syphilis from the case morbidity file and 2) not all cases of chlamydia pneumonia or opthalmia were linked to a woman who was identified as having the infection either on the case morbidity file or from laboratory tests. Five of those in the study sample with latent syphilis were low birth weight.

Among all women in the relational database identified with syphilis during the time parameters as appropriate to her individual pregnancy, 20% (5/24) of those with primary or secondary syphilis had a low birth weight event compared to 11% (30/261) with latent syphilis. Of the nine syphilis and fetal death linked records, none were low birth weight.

Closer scrutiny of the syphilis cases in the database revealed that 14% received treatment outside of the standard parameter of 14 days from diagnosis, and 17% never received appropriate treatment for the stage of disease. The majority of all these cases were not reported into the case morbidity system within the standard of 14 days from test date to report date.

Information regarding trimester of initiation into prenatal care was available from the Healthy Start prenatal screen on 63% (186/295) of the women with syphilis. For these women, all but 11.8% entered prenatal care, 48.3% in the first trimester, 29.6% in the second, and 10.2% in the last trimester. Among the women in the study sample, the distribution was different, with 54.3% entering in the first trimester, 37.1% in the second, and 8.6% in the third semester. Dual infection with chlamydia and gonorrhea was present in 8.4% of the study sample; this rate is fourteen times that observed in the statewide prevalence estimate based on all public health laboratory chlamydia and gonorrhea test results during 1996. It is nearly seventeen times the rate observed among the prenatal specimens. Table 20 below summarizes the STD related finding from this study.

Table 20. Comparison of Odds Ratios in the Study Sample for Different STD Variables and Adverse Birth Weights.

Low Birth Weight	**OR**	**p value**
Chlamydia positive, adjusted for inadequate weight gain	1.98	0.0184
STD's past or present, with all variables	1.48	0.0278
STD's past or present, without any race indicator	1.70	0.0029
STD's past or present, among women of black race	1.78	0.0046
Term Low Birth Weight	**OR**	**p value**
Gonorrhea positive, adjusted for adequate weight gain	5.11	0.0025
STD's past or present, with all variables	1.79	0.0075
STD's past or present, without any race indicator	2.01	0.0029
STD's past or present, among women of black race	2.24	0.0073
Pre Term Low Birth Weight	**OR**	**p value**
Chlamydia positive, adjusted for inadequate weight gain	2.34	0.0099
STD's past or present, without any race indicator	1.65	0.0362
STD's pat or present, among women of black race	1.72	0.0383

Outcome of Research Question

The research question: What association(s) exist(s) between low birth weight and *Chlamydia trachomatis* infection during pregnancy?

- A significant association at the unadjusted level was found for chlamydia infection in pregnancy for low birth weight and for pre-term low birth weight. Women with *Chlamydia trachomatis* during pregnancy would have more than an 80% increased probability of low birth weight and pre-term low birth weight based on these findings alone.
- After adjusting for other independent risk factors and inadequate weight gain, a significant association was found for chlamydia infection in pregnancy. The association at 95% confidence interval was OR 1.99, $p < 0.02$ for low birth weight, and OR 2.34, $p < 0.01$ for pre-term low birth weight in this study. In contrast to the pilot study on which this study was modeled, the strongest association was found in term low birth weight infants, OR 2.50, $p < 0.0000$.
- The chlamydia positivity observed in this study sample derived from women who received their care from county health depatments is less than one half that observed in the prenatal county health department population from which the laboratory data set was constructed and subsequently linked to the 1996 birth and fetal death records.

CHAPTER 5
DISCUSSION AND RECOMMENDATIONS

The purpose of this study was to examine, using a larger sample size, the research question originally posed in a pilot study conducted by this investigator and colleagues in 1997, of 2,885 birth records and *Chlamydia trachomatis* test results. The present larger study, with 191,988 birth and fetal death records, was designed to examine potential associations between *Chlamydia trachomatis* and low birth weight outcomes among a population-based sample of pregnant women and adolescents, who initiated prenatal care through county health departments.

Additional variables were sought for the present study to better control for confounding risk factors. A relational database was constructed that linked birth and fetal death records, Healthy Start prenatal screens, maternal and infant sexually transmitted case morbidity, maternal and infant laboratory test results, and congenital syphilis case records. In this chapter, an analysis of the study question and other findings of interest, implications for clinical practice, implications for public health policy, and suggestions for future research will be discussed.

Analysis and Discussion of Research Findings

This retrospective epidemiologic study identified a significant statistical association between chlamydial infection during pregnancy, and low birth weight, and pre-term low birth weight. The findings are the result of analysis conducted on a large sample size (14,002 records) of retrospectively gathered information, and is not a statement of cause and effect relationship, or direction of sequence of events. The study findings are robust, considering the significant number of other factors reported to increase the risk for low birth weight that were controlled for in the logistic regression models. The substantial associations observed in the final two logistic regression models will be discussed in more detail, along with other associations observed, in the initial four models.

The finding of significant associations in this study between chlamydial infection during pregnancy and low birth weight, add further evidence to the body of earlier work reported by Ryan et al., Gencay et al., Gravett et al., and Martius et al. as discussed earlier. Additionally, this is the second study conducted among pregnant women who received their prenatal care in county health departments to identify a strong association between low birth weight and *Chlamydia trachomatis*.

The descriptive analyses highlighted differences and similarities between the study population and the statewide birth and fetal death cohort for 1996. The rate of low birth weight was less at 6.9% compared to 8.1%. The term low birth weight rate was slightly higher (2.6%, 2.4%) and the pre-term low birth weight rate was also lower at 3.5% compared to 4.8%. Fewer women in the study sample were infected with chlamydia than

was observed statewide among women who received their prenatal care at the county health departments during the same time period (2.0%, 5.5%).

Key among the independent variables at the bivariate level, was the significant association between many of them and low birth weight. The study question variable, chlamydia infection, was significant at all levels of low birth weight, indicating nearly two-fold the risk of low birth weight among, infected pregnant women; unadjusted odds ratios at the 95% confidence interval were 1.88, 1.87 and 1.86 with p values 0.00, 0.03, and 0.01, respectively. Other traditionally reported risk factors such as smoking, inadequate weight gain, black race, and history prior poor birth outcomes, were also significant. Of interest was the protective association of stress and of not having completed high school. Noteworthy, was the statistical significance of gonorrheal infection and the pooled infection of other sexually transmitted infections; these were higher than smoking, chlamydia, and race.

An unanticipated finding for this researcher was the persistent and very significant association between inadequate weight gain and low birth weight. This association remained in each of the first four logistic models and across all ranges of low birth weight. The adjusted odds ratios at 95% confidence interval ranged from a 'low' of 2.27 ($p \leq 0.0000$) among women of black race/ethnicity with low birth weight to a 'high' of 3.75 ($p \leq 0.0000$) among women of white race/ethnicity who delivered a pre-term low birth weight infant. The highest significance within each of the four models was with pre-term low birth weight. Most other studies examining the association between weight gain and pre-term delivery have identified an increased risk ranging from 50% to 100% among pregnant women with inadequate weight gain (Carmichael & Abrams, 1997). Overall, the

risk in this study for a pre-term low birth weight was significantly higher for women with inadequate weight gain. The initial four logistic models identified associations between low birth weight and select risk factors.

Analysis suggested that inadequate and adequate weight gain contributed a strong confounding influence. Once this was controlled for, different patterns of associations were observed. Of particular interest was the regrouping of independent variables. Maternal age, black race, smoking, use of alcohol, and gonorrhea infection increased the likelihood of different levels of low birth weight among women with adequate weight gain (OR 1.43, 2.33, 1.87,1.63, and 5.11, respectively). Among women with inadequate weight gain, infection with chlamydia was found to be statistically significantly associated with the dependent variables (OR 1.98 for LBW, and 2.34 for PTLBW). Other factors that contributed to increased likelihood of low birth weight events among women with inadequate weight gain, were use of alcohol (OR 2.36), prior poor pregnancy outcomes (OR 1.96), smoking (OR 1.76), black race/ethnicity (1.51), and not being married (OR 1.37). Other researchers, who have reported their work in the literature, have not reported these same patterns of association, perhaps due to the more limited numbers of variables included in other studies. Controlling for level of weight gain increased the significance of chlamydia infection, gonorrhea and a history of other sexually transmitted infections.

The pathogenesis of chlamydial infection in pregnancy and low birth weight is not well understood. Three models were discussed in Chapter 2: 1) delayed-type hypersensitivity, 2) inflammatory response mediated by human-heat shock proteins and chlamydial heat shock proteins, and 3) genetic susceptibility (Chlamydia Genome Project, 1999). Two 1996 studies of the immune consequences of Chlamydia trachomatis have

demonstrated a correlation between inflammatory cytokines, chlamydial heat shock proteins, IgG, IgA, and poor pregnancy outcomes. Askienazy-Elbhar (1996) suggests that infection-activated T-cells may send the wrong message to developing embryos, disrupting the balance between pro- and anti-inflammatory cytokines and leading to suppression of embryo rejection by maternal tissue and to impaired embryo growth. Neuer and colleagues (1996) examined first trimester decidua and identified heat shock proteins (hsp), 27, 60, 70 and 90 in stromal cell, endometrial glands and leukocytes. They conclude that prior sensitization by chlamydial human shock protein (hsp) may lead to over production of hsp-sensitized leukocytes and introduction of inflammatory responses, which will disturb the embryos growth.

Morrison (1996) noted that IgA antibodies appear to promote resistance to reinfection, while cell-mediated immunity promotes resolution of established infection. However Schachter (1995) noted that while chlamydial infection results in abundant humoral, secretory and cell-mediated immune responses, the actual role in the development of resistence to infection is not clear. The predominant antibody produced in response to uncomplicated chlamydial genital infection is IgA. The fetus is unable to mount an adequate IgA or IgG response and is thus almost entirely dependent on IgM for its primary immune response. Active transport of IgG is mediated by surface receptors on trophoblastic cells to move immunoglobins from maternal to fetal circulation. Successful transport would appear to be key to fetal resolution of intrauterine infection. Koehler et al. (1996) presented data that "show chlamydia-infected human blood monocytes are viable within the host cell, even though the infection is non-replicative and arrested at some point in the life cycle," and the authors suggest that the metabolically active chlamydiae may

contribute to sustained inflammatory response. Others report that this sustained inflammatory response may remain asymptomatic, with infants regularly infected as demonstrated by transplacental passage of IgG antibodies collected from cord blood in infants who remained symptom free for the first week of life (Djukie et al., 1998).

While the research remains conflicting, it has been suggested that a pathogenesis model of inflammatory response would explain apparent persistent chlamydiae presence, as well. Beatty, Morrison and Byrne (1994) observed the presence of chlamydial antigen and nucleic acids in culture negative specimens. Viable RBs may retain the capability to stimulate immunopathologic changes, yet remain non-replicating. Bragina and Gomberg (1998) observed atypical cytoplasmic inclusions in individuals where infection persisted after unsuccesful antibiotic therapy. They noted that their latency could be distinguished from persistency by the failure to demonstrate any metabolic processes. They suggest this phenomenon of morphologically changed chlamydial bodies as a possible explanation for persistence. As noted in a prior section, Dean and colleagues (1998) provided compelling evidence of long-term persistence through analysis with *omp1* genotyping. In contrast, Workowski and colleagues (1993) maintained that persistence did not follow adequate treatment.

Immunity to most etiologic agents associated with sexually transmitted infections remains poorly defined. Researchers have observed that the younger the patient, the greater the likelihood that any given infection will be a primary infection. Brunham et al. (1990) have suggested that it is likely that, in general, primary infections in a non-immune host cause the greatest morbidity. In the study population, the rates of chlamydial infection were significantly higher among the youngest of adolescents, as was low birth weight;

however the number was small. Investigations employing animal models have demonstrated a difference between initial and recurrent infection response of the host. In the initial infection, polymorphonuclear leukocyte reaction is the predominant response, while mononuclear cell response is favored in recurrent infection (Martin, 1990).

Papiernik and colleagues (1998) suggest that infection during pregnancy may be the result of multiple related factors such as cervical length and the presence of multiple bacterial infections. The findings of this study suggest that while an association may exist between intractable LBW rates and persistent chlamydial infection, the pathogenesis and causal mechanism remains elusive. However, the significance of the association identified, and the prevailing literature on pathogenesis suggests, that there is indeed a complex association between *Chlamydia trachomatis* and intra-uterine fetal growth. There is need for further study in this area to better understand the pathogenesis during pregnancy, in order to effectively intervene during the process.

This study did not explore the possible effect of other cervical infections that may have been present in the study population and which have previously been linked in the literature to poor pregnancy outcomes (McGregor & French, 1991; Brunham, Holmes, & Embee, 1990). Harrison et al. (1983) made the important point that the presence *of Chlamydia trachomatis, Ureplasmaurealyticum* or *Mycoplasma hominis* is a sign that one of the other organisms is also present. In this study, an exceptionally high rate of dual infection was noted with gonorrhea. Additionally, no information was available regarding the treatment received by chlamydia infected women in this study sample, or the trimester in which treatment, if any, was received.

The true efficacy of different antibiotics used to treat chlamydia and other STDs during pregnancy is unknown. Little evidence exists in the literature that any of the currently recommended treatments have been researched in controlled clinical trials among non-pregnant females, and even less in pregnant females. These studies often used tests with low sensitivity, and did not examine drug absorption or pharmokinetics simultaneously (Bush, 1994; Turrentine, Troyer, & Gonik, 1994). Earlier work by researchers has suggested that treatment of chlamydial (and other) infections in pregnancy has reduced low birth weight rates in the populations studied (Hillier et al., 1995; McCormick, 1987; McGregor et al., 1997; Schachter et al., 1986; Hauth, Goldenberg, Andrews, Dubard, & Copper, 1995). However, again these studies often used tests with low sensitivity, and did not examine drug absorption or pharmokinetics simultaneously.

Information exists concerning altered pharmocokinetics in pregnancy leading to physiologic changes in absorption, distribution, hepatic metabolism, renal elimination, and transplacental passage of some drugs (Dashe & Gilstrap, 1997). For example, increases in blood volume and creatinine clearance lead to lower serum concentrations of many antibiotics. Clearance of cephalosorins appears to be increased during pregnancy, probably due to increased renal blood flow and decreased protein binding (Meyer, 1995). Ceftriaxone has a shorter half-life in pregnancy, yet ceftriaxone, a third generation cephalosorin is the drug of choice for gonorrhea. It is prescribed at one universal dosing level according to national guidelines regardless of pregnancy status (Dashe & Gilstrap, 1997; CDC, 1998b). Gonorrhea untreated in pregnancy, can cause serious complications for both the mother and the infant, including markedly increased risks of disseminated infection and preterm birth.

National guidelines for the management of syphilis state that treatment should be dosed at an appropriate regimen for the stage of the disease (CDC, 1998b). These same guidelines do not alter the dosage for pregnant women at different stages of infection. Plasma concentrations of penicillins are reduced during pregnancy. This is believed to be the result of increased glomerular filtration and increased renal blood flow. Researchers recommend penicillin dosages be increased by 50%, especially for severe infections, except for in the last trimester (Meyer, 1995). Infection with *Treponema pallidum* in pregnancy is not generally described in the literature as a "severe" infection. However, the birth of an infant with congenital syphilis has long been designated as a sentinel public health event, suggestive of a failure in the community health system.

This study identified strong associations between pooled STDs and low birth weight, and also high rates of low birth weight among women with a history of either infectious or latent syphilis. Additionally, findings from this study suggest that not all women with syphilis received either appropriate or timely treatment for the time period examined related to their pregnancies. Other researchers have identified similar patterns of association between missed infections and no treatment or inadequate treatment, according to prevailing standards (Reyes, Hunt, & George, 1993). Christian, Lavelle and Bell (1999) reported on several preschoolers with probable intra-utero acquired syphilis that was not identified earlier. Nathan et al. (1993) demonstrated a wide range of penicillin levels in different maternal and fetal compartments. Dorfman and Glaser (1990) of New York City, reported on seven congenital syphilis cases first identified at 3 to 14 weeks of age, secondary to the development of symptoms. Four of the infants and their mothers were seronegative at delivery, and the other three were not tested at delivery, since the

mother was seronegative during the pregnancy. With the presentation of multi-systemic disease, each maternal-infant pair was found seropositive upon testing. Berry and Dajani (1992) reported similar patterns of events that occurred in Michigan and involved 18 infants (35% of the cases reported over the five-year period from 1986 to 1990). Numerous groups of researchers have also discussed the challenge of accurately detecting neonatal infection with the commonly available serologic tests for syphilis. Stroll et al. (1993) and colleagues studied three different assays in a population of 116 neonates and concluded, "no single diagnostic test was sufficiently sensitive to use alone for treatment decisions." Even the highly sensitive polymerase chain reaction technology is reported at only 78% sensitivity for congenital syphilis specimens (Grimprel et al., 1991). These studies highlight several issues that require additional consideration: 1) consistent application of serologic screening at delivery for syphilis; 2) appropriate management and treatment according to guidelines; and 3) more sensitive tests to detect incubating or early infection in pegnant women and neonates.

Galan, Montalvo and Deaver (1997) reported that only 61% of pregnant women sustained a positive response to recommended treatment dosages of penicillin during their pregnancies, concluding that under-treatment may be more common than realized by clinicians. Two recently published studies have reported similar delays in treatment for chlamydial infections. One group reported a median duration of 21 days from positive test results to treatment (Foglia, 1999) Others demonstrated delays of more than two weeks for 30% and no treatment for another 20% (Schwebke, Sadler, Sutton, & Hook, 1997). Earlier work with infertility and pelvic inflammatory disease has demonstranted a strong association between delayed treatment and more severe damage to reproductive structures

(Hillis et al., 1993). Perhaps an association exists between chlamydia pathogenesis and the timing of treatment. This question merits further study.

The distribution of inadequate weight gain indicated that fewer women of black race/ethnicity were underweight when compared to women of white race/ethnicity. Black women were more likely to be of either high or obese body mass index. A greater percent of black women were obese among women over 34 years of age. Other researchers have reported this same finding. Among the very youngest of mothers, (129 records $\leq$ 14 years) more black women were underweight, 69.1% compared to 30.9%. It was this same age group that had the highest rate of low birth weight, 12.7% in the study sample. It was also among this younger age group, those under 14 years of age, that the rate was highest, with 42.6% of 129 young women underweight. Scholl and colleagues (1992) reported an adjusted odds ratio of 5.74 for small-for-gestational-age, among adolescents of younger age and low pre-pregnancy body mass. The interactions between maternal age and pregnancy weight gain remain to be explored with this data.

No information was available in this relational database to identify if these adolescents were less than two years postmenarche. Some conflicting research has suggested that a potential association may exist between the interval from menarche, onset of pregnancy and a metabolic state of developmental growth in the very young adolescent (Suitor, 1997; Institute of Medicine, 1992). Additionally, some research suggests that the very young pregnant women may be at a higher risk of a slow rate of weight gain during pregnancy (Institute of Medicine, 1992). Maternal eating disorders such as anorexia nervosa, bulimia and bulimia nervosa, place a woman at increased risk of weight gain abnormalities (Institute of Medicine, 1992). No information was available within this study

data set to evaluate these and other behaviors or conditions that may have contributed to the strength of the observed association between inadequate weight gain and low birth weight.

Other maternal medical conditions may confound or amplify the risk of low birth weight in women with less than ideal weight gain during pregnancy. For example, iron deficiency anemia may increase the risk of inadequate weight gain in the first and second trimesters (CDC, 1999b). Data from the 1996 Pregnancy Nutrition Surveillance System, suggested that 40% of black women and 29% of all women had anemia in the third trimester. While history of maternal medical conditions were controlled for in this study, closer examination of the interactions between anemia and other medical conditions such as preeclampsia, body mass index and weight gain are warranted. Particularly in light of reported low levels of reporting on medical risk factors observed by researchers (Woolbright & Harshbarger, 1995; Woolbright, Hilliard, Harshbarger, & Wertelecki, 1999).

Smoking was strongly identified with all levels of low birth weight events among women with less than recommended weight gain in this study (OR 1.76, OR 2.35 and OR 1.67). Data from the Healthy Start prenatal screen tobacco use indicator, revealed women in this sample were smoking at a similar rate as pregnant women surveyed nationally, 29.4% compared to 23-37% in the Pregnancy Nutrition Surveillance System (CDC, 1999b). Between those identified from the birth record as having ever smoked, and those identified from the Healthy Start prenatal screen as having used tobacco in the last two months, the rates of low birth weight were similar (8.2% and 7.0% respectively). This rate

is significantly lower than the rate reported by the Prenatal Risk Assessment Monitoring System for the following year in Florida, 18.2% (CDC, 1999c).

Hickey and colleagues (1997) found in their study that women of black race/ethnicity were twice as likely to experience low prenatal weight gain with a mistimed pregnancy than those who reported that the timing of their pregnancy was acceptable, or who were of another race/ethnicity. In the present study, this finding was not confirmed. Among black women who reported that the timing of their pregnancy was acceptable, 24.7% had an inadequate weight gain compared to 26.8% who reported that their pregnancy was mistimed. When inadequate weight gain was examined within the context of other independent variables such as inter-pregnancy interval, it was observed that both women of white or black race/ethnicity with inadequate weight gain (20%) were equally affected by a relationship between short inter-pregnancy interval and low birth weight. The two groups of women had similar rates of low birth weight, 12% and 12.7%. Rawlings et al. (as cited in Institute of Medicine, 1992) found a more pronounced difference between the two racial/ethnic groups. He and colleagues reported an increased risk for white women only, with short inter pregnancy interval of three months compared to black women for nine months. The differences observed between race/ethnic groups and inter-pregnancy intervals, merit further analysis to identify their significance. Equally important would be further analysis to gain more insight into why the observed increased risk for low birth weight associated with inadequate weight gain appeared to affect white women more than black women in the logistic modeling. A recent unrelated study looking at mortality and body mass index, observed that black men and women had lower risks of death with

the highest body mass index group, suggesting that associations with health outcomes may be wider than those observed in this study (Calle, et al. 1999).

Fetal and infant mortality review projects completed within Florida, have reported obesity and poor nutrition among the top five factors most commonly present in cases of fetal and infant deaths occurring in Florida (Bellamy, 1998). A similar finding was not supported by this study for fetal deaths. Overwhelmingly, more than half of the fetal deaths occurred to women with normal body mass index and adequate weight gain during pregnancy. Among those who did not gain enough weight, already underweight women were most adversely affected; however, the numbers are very small.

Several researchers have suggested that the maternal self-report of their pre-pregnancy weight, and their total weight gain in the pregnancy may have biased the findings (Yu & Nagey. 1992; Schieve et al., 1998; Hickey et al., 1996). They also discuss the work of others who have observed that self-reported weight measures correlate well among non-pregnant women, and that under and average weight women are less likely to underreport than are obese women.

Inadequate prenatal care visits was not a strongly associated risk factor in this population. Some recent literature has suggested that the "counting" of prenatal visits has not demonstrated a clear association of benefit in reducing adverse pregancy outcomes. It is plausible that records within this data set had incomplete information regarding timing and adequacy of visits. Other studies have demonstrated overall accuracy to be as low as 14.3% when birth cetificate and medical records are compared (Clark, Fu, & Burnett, 1997). Similarly, error may have occurred in the coding of birth weight (Bruskill, 1990).

This phenomenon was suspected with the observation of extreme outliers noted during analysis, and addressed in the methodology applied.

One area of analysis that highlighted ongoing discussions in the literature was race and ethnicity. Aspinall (1998) provides a comprehensive review of several concerns regarding the use of race as a risk factor. While he suggests that ethnicity may be a more suitable way to categorize individuals within the context of a study, he observes that it is equally subject to flaws. In this study, there was an apparent discrepancy noted between the coding of infant race, based on maternal and paternal distribution, and coding rules. As noted in the prior chapter, ethnicity was hardly all encompassing due to a very restrictive list of options available to those who enter the data. When the data in this study was examined without regard to race, the scope of associations between the independent variables and low birth weight was greater than in subsequent logistic models when race and weight gain were controlled for. Simiarly, different patterns of association were noted when women of white and black race were compared. Perhaps race as a variable in this study is merely a marker for other contributory factors such as poverty. Rabin and others (as cited by CDC, 1993) make this same suggestion.

Implications for Clinical Practice

The significant associations observed in this study between chlamydial infection in pregnancy and low birth weight, suggest numerous opportunities to positively impact on clinical practice. For example, urine-based tests for chlamydia and pregnancy should become the standard practice for screening young reproductive age women who receive or seek routine health care services while participating in school related sports activities, e.g.,

the required sport physical. The same practice would enhance identification of asymptomatic infections among incarcerated juveniles and young women, and adolescents who seek routine immunizations. Nurse practitioners, who work in family practice and primary care settings, should incorporate chlamydia screening (and other STD screening) along with improved sexual history elicitation into the preventive health and acute care encounter with young women. This may require the revision of practice guidelines to reflect the findings and content discussed in this study.

Establishment of multi-disciplinary collaborative case conferences, focused on sexually transmitted infections during pregnancy, may assist county health departments and their private community partners to better identify missed opportunities for identification of early chlamydial infection and to provide timely treatment. Included in these collaborations should be advanced practice nurses, certified nurse midwives, physician assistants, infectious disease specialists, and disease investigators from both private and public settings.

Other significant associations observed in this study between low birth weight, and gonorrhea and syphilis, suggest numerous opportunities for nurse practitioners to positively impact on clinical practice. For example, a urine pregnancy test should appropriately be performed on all women with reactive syphilis serologies in the absence of documented proof of sterilization or hormonal implants. The opportunity to identify an early pregnancy in a woman with syphilis could both increase the likelihood for adequate, and timely treatment, and also increase the outreach activities to identify all potential partners and sources of re-infection during the pregnancy.

The implications for intervention in the spread of chlamydia , syphilis, and gonorrhea infections go beyond the clinical setting. Additional training on the elicitation of complete sexual behavior, menstrual and obstetric histories should be provided to nurses, advanced practice nurses, and other health professionals such as STD disease investigators, who work in settings where contact with reproductive age women is likely. Provision of such training might serve to raise the index of suspicion of infections associated with pregnancy, and thus assist public health department clinicians and health professionals to better identify associations between STDs and adverse pregnancy outcomes such as fetal deaths, spontaneous abortions, and altered menstrual patterns that are suggestive of chlamydial infections.

The findings related to inadequate weight gain suggest several implications for change in the way that prenatal nutritional services are delivered. At present, women are provided nutritional counseling and risk assessment when they are enrolled into the WIC program. Generally, there is no further evaluation of a woman's individual progression toward the desired weight gain in pregnancy by a nutritionist. Nurse practitioners and certified nurse midwives should continue to intervene with nutrition counseling. In light of the persistent association identified between inadequate weight gain and low birth weight, term low birth weight and pre-term low birth weight, implementation of interim nutritional monitoring sessions would provide an opportunity to pose appropriate interventions earlier than in the post-partum period following the adverse pregnancy outcome. Therefore, advance practice nurses should refer pregnant women with slow or undesirable weight gain to the nutritionist, for collaboration on the development of a nutritional plan

that would appropriately address eating behaviors, eating disorders, access to the needed food groups, and instruction on preparation of nutritionally valuable meals.

Implications for Public Health Policy

A relational database of the size developed for this study is a labor-intensive initiative. It is also a powerful tool for examination of numerous public health issues and problems from the vantage of different program priorities. It would be advantageous for the Florida Department of Health to assure that common demographic information contained in the many data systems used in this study be standardized, in the future, to support more relational database analyses. This will entail simultaneous development of coding, file layout for the fields and conversion programming to support the transmission of data files to different federal agencies, e.g., National Center for Health Statistics, The Centers for Disease Control and Prevention. These same federal agencies also do not share standard coding of variables such as race, ethnicity or counties between offices within their own agency or with other federal agencies involved in the collection of health related data.

Future computerized data systems should be developed with all the input of all parties that might want to utilize the data. While data systems are developed to support particular program goals, statutory requirements, or the evaluation of services, the involvement of prospective users of the data could greatly enhance the benefits to program goals, evaluation and reduce costs in recognition of unproductive services through better analyses. A Department of Health-wide ongoing cross-disciplinary work group focused on

reproductive health care, might be an appropriate avenue to routinely review the suitability of data systems to support analyses from linked and relational databases.

Schools of nursing should strengthen course work on data management and information in order to prepare advanced practice nurses better for future involvement in the decision analysis process. Future advanced practice nurses will need to acquire more sophisticated skills in the area of data management at the clinical level as well as interpretation of clinical evidence and epidemiological reports. This will be integral in order for nurses to more fully participate in collaborative work group activities aimed at the development of new data systems that will support analysis of evidence-based clinical nursing and medicine.

The sexually transmitted disease case morbidity system merits closer scrutiny to evaluate the capacity of the system to support future examination of the reproductive outcomes sustained by women infected with STDs. To effectively capture the full reproductive history of women in the childbearing years, additional fields should be developed within the case morbidity system. A designated field(s) is only a part of the answer. A field must be accurately completed to be useful for future analysis that will provide insight into the relationship(s) between chlamydia, and other sexually transmitted infections and pregnancy outcomes. Another change to the surveillance system that might assist regional area STD Managers, would be an automatically generated report that would alert surveillance staff regarding the percentage of cases with unacceptable test to treatment intervals. Such reports may heighten awareness among county health department staff regarding the need to educate select community providers on appropriate treatment intervals and stimulate identification of the barriers that contribute to the

delayed time frames. Automatically generated flyers on treatment guidelines (or updates) could be mailed to nurse practitioners and physicians who did not use treatment options recommended by national guidelines for sexually transmitted infections. If these and other reports are shared directly with nurse practioners and physicians, disease investigators will have additional opportunities to offer their services for partner elicitation and notification to the clinicians. Similarly, other system changes could alert county health department staff when any reported STD case involves a woman who is pregnant. This may assist to reduce re-infection of the pregnant woman through increased awareness among county health department staff regarding the need to more rapidly locate any untreated partner(s) and document treatment.

Evidence in this study suggested a much wider involvement of syphilis in adverse pregnancy outcomes. None of the women identified with low birth weight, who were also infected with late syphilis, were identified as pregnant in the case morbidity system. However, all except one of the women, who sustained a fetal death while infected with syphilis, was identified within the case morbidity system. This variability of reproductive health related data suggests that an independent evaluation of the quality of the case morbidity information and subsequent documentation on field and medical records should be considered. Quality assurance audits on the entry of case data entry into the STD*MIS should be regularly scheduled, and conducted at all levels of data entry, to better ascertain potential discrepancies in demographic data.

The fetal death certificate does not presently provide a field for reporting of syphilis diagnosis in the mother during pregnancy. Stillbirth is highly associated with syphilis infection during early pregnancy and continues at a reduced rate throughout the

pregnancy. While medical records personnel can enter this condition in the "other" space provided, the reality is that the word "syphilis" might raise the index of suspicion and increase the likelihood that a specimen for serology would be taken, or that the information contained in the woman's medical history would improve reporting of undetected cases. Ideally, this change should occur at the national level, as the state fetal death certificate is modeled on the national standard certificate.

Nationally, syphilis is at an all time low and intensive efforts are underway to eliminate syphilis by the Year 2004. A heightened level of awareness in the provider community might help achieve this goal. This may be attained through numerous measures: 1) multi-disciplinary analysis of syphilis case data in the community by nurse practitioners, physicians, disease investigators and others; 2) an emphasis on dissemination of findings related to cases that represent multiple missed opportunities for intervention; 3) dissemination of information to community clinician providers regarding their legal requirements to screen during the first and third trimesters, and at delivery as indicated; and 4) dissemination of current information about the clinical manifestations, diagnostic classification and treatment guidelines to advanced practice nurses, physician assistants, and physicians.

Clinicians routinely participate in fetal death and infant mortality review teams. Numerous findings from this study would suggest that the participation of advanced practice nurses, infectious disease specialists, or disease investigators knowledgeable in both sexually transmitted disease prevention activities and women's reproductive health, might assist to identify other patterns of association and gather the appropriate documentation.

Internet web-based case reporting of sexually transmitted infections may provide another venue and support an increased index of suspicion for sexually transmitted infections among clinicians. Such an approach would require that the appropriate changes be made, in the future, to those Florida Statutes that now direct the reporting of STDs exclusively through the county health department. Such a model would also provide an opportunity to collect negative test result denominator data, for use in calculation of statewide chlamydia prevalence rates (and that of other sexually transmitted infections). Activities of this type would provide support for the development of active surveillance systems for sexually transmitted infections.

The findings in this study suggest that there are potential economic implications from intra-pregnancy infection with chlamydia and other STDs. Examination of these relationships has been reported by Mittendorf and colleagues (1994). They utilized a calculation of population attributable risk based on prevalence of the infection in the population and the odds ratio associated with increased likelihood of low birth weight from chlamydial infection. Previously, this researcher applied this same methodolgy to the findings from the pilot study on which the present work was modeled. These calculations resulted in a cost avoidance estimate of 3.7 million dollars for low birth weight infants born during 1995, attributable to universal screening and treatment for chlamydial infections during pregnancy (Florida Department of Health, 1997c). At a future time, the economic associations related to the findings in this study should also be analyzed, in order to estimate cost-benefit and cost-effectiveness through chlamydia screening. The implications for public health policy development regarding population-based screening for chlamydia (and other STDs) may be significant.

Significant associations were identified in this study that utilized a chlamydia test with less than ideal sensitivity. This would suggest that policy makers should consider identification of funding to support distribution of more sensitive testing methodologies through county health department clinics. The cost to the community from low birth weight is significant; there are both financial and health related costs for the individual family and the affected infant.

The findings from this study should be disseminated to policy makers associated with regional prenatal care coalitions, community nurse practitioners, physicians and physician assistants, to county health department staff and to the general public. Additionally, the information contained in this study should provide valuable stimulus to foster other research projects among current students of advanced practice nursing. Suggested future research topics follow below.

Implications for Future Research

Numerous interesting future research avenues are suggested by the findings in this study. First, stratification by socio-economic status through the use of geocoding, census data and fee eligibility determination data linked to the study database, should be the next analysis. Closer examination of treatment information contained in this database, as well as enhancement with treatment records for women infected with chlamydia would provide opportunity to clarify some questions raised during the analysis. Linkage of pending Medicaid files to the study database should be completed in order to support more comprehensive analyses with the existing database. And sometime in the future, another

attempt at the original research question should be made with improved databases from the 1997 or 1998 birth years and more laboratory test results!

The finding of significant relationships between low-birth-weight fetal deaths and late syphilis cases, that were not previously identified as such, suggests that closer scrutiny of the data and risk variables within the database would be an appropriate analysis to conduct. It would also be useful to link the males identified as infected during the same time period to the birth and fetal death records in order to examine their possible association with fetal death and low birth weight events.

An analysis of the relationship between records identified as complicated by herpes at the time of delivery, and low birth weight, or other fields from the Medicaid database would provide potentially very useful insights. Linkage between this study's relational database and other HIV/AIDS databases would provide opportunities for ecological analyses of related sexual behavior patterns among young reproductive aged women and rates of adverse pregnancy outcomes.

Closer examination of inadequate weight gain, body mass index, fetal deaths and published risks related to adverse pregnancy outcomes may identify new findings of interest in this population. Analysis of the level of WIC services in the study population compared to the larger group for women with inadequate weight gain may provide useful insights for programmatic evaluation. Adolescent outcomes identified in this study suggest other questions such as: 1) is the role of insurance coverage and entry into care, related to rates of STD infection and low birth weight among adolescents? 2) is there an association between weight gain during pregnancy, young maternal age and adverse birth outcomes? or 3) would underweight adolescents' pregnancy outcomes benefit from closer scrutiny of

gestational weight gain? In future years, an analysis comparing sub-samples of births and fetal death records for adolescent and young adults infected with sexually transmitted infections, would provide an opportunity to explore more fully a group at high risk for STD related adverse outcomes, and other socially related events.

The many statistically significant findings from this study suggest the need to examine a much larger sample to better understand the association between chlamydia, gonorrhea, and syphilis infection and low birth weight. A large multi-centered, and multi-disciplinary randomized prospective, designed to examine the contributory role of each STD while controlling for the others, would be invaluable if highly sensitive tests and all infections were included. Ideally, such a study would also control for the many low birth weight risks examined in this study, as well as other behavior risk factors not available within the present relational database. It would also include the diverse professional perspectives of laboratorians, advanced practice nurses, physicians, and biologists, utilizing both quantitative and qualitative analyses to more fully examine the associations between low birth weight, chlamydia and other sexually transmitted infections. There is clearly a need to better understand the pathogenesis of *Chlamydia trachomatis* in pregnancy to effectively intervene in the process.

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APPENDIX A

VARIABLE LIST

Appendix A. Variables List.

Original Variable Name	New Variable Name	Variable labels
D_R	D_R	record number
CDOBM	CDOBM	child's dob month
CDOBD	CDOBD	child's dob day
CDOBY	CDOBY	child's dob year
BFNUMBER	BFNUMBER	bfnumber
CERT_NO	CERT_NO	cert_no
CSEX	CSEX	child's gender
CRACE	CRACE	child's race
PLURAL	PLURAL	plural birth
APGAR1	APGAR1	apgar score at 1 minute
APGAR5	APGAR5	apgar score at 5 minutes
BW	BW	birth weight
MRACE	MRACE	mom's race
MMS	MMS	mom's marital status
MED	MED	mom's educational level
MAGE	MAGE	mom's age
MBST	MBST	mom's state of birth
MRCNTY	MRCNTY	mom's county of residence
MRLIM	MRLIM	mom's lives within city limits
STATE	STATE	mom's state
MDOBM	MDOBM	mom's dob month
MDOBD	MDOBD	mom's dob day
MDOBY	MDOBY	mom's dob year
MHSIP	MHSIP	dad's hispanic ethnicity
FAGE	FAGE	dad's age
FBST	FBST	dad's state of birth
FRACE	FRACE	dad's race
FED	FED	dad's educational level
FDOBM	FDOBM	dad's dob month
FDOBD	FDOBD	dad's dob day
FDOBY	FDOBY	dad's dob year
FHISP	FHISP	dad's hispanic ethnicity
ESTGEST	ESTGEST	estimated gestation
TOBUSE	TOBUSE	tobacco use during pregnancy?
CIGS	CIGS	average number of cigarettes per day
ALCUSE	ALCUSE	alcohol use during pregnancy?
DRINKS	DRINKS	average number of drinks per week
WTGAIN	WTGAIN	weight gained during pregnancy
MHF1 - 17	MHF1 - 17	medical history factors for this pregnancy
MOD1	MOD1	vaginal delivery
MOD2	MOD2	vaginal delivery post prior c-section
MOD3	MOD3	primary c-section delivery
MOD4	MOD4	repeat c-section delivery
MOD5	MOD5	forceps delivery
MOD6	MOD6	vacuum delivery
PRENL	PRENL	number of live births now living
PREND	PREND	number of live births now dead
LLBM	LLBM	month of last live birth
LLBY	LLBY	year of last live birth

Appendix A. Continued.

Original Variable Name	New Variable Name	Variable labels
DOTM	DOTM	year of last other terminations
DOTY	DOTY	year of last other terminations
PRETER	PRETER	number of total other terminations
LMPM	LMPM	lmp month
LMPD	LMPD	lmp day
LMPY	LMPY	lmp year
PREMO	PREMO	month prenatal care began
PREVIS	PREVIS	number of prenatal visits
BFD_A	BFD	b or fd designation for birth record
BWG	BWG	birth weight group
LMPDAYS	LMPDAYS	calculated total lmp days
GWEEKS	GWEEKS	total gestation weeks
CDOBDAYS	CDOBDAYS	total gestational days for formula
GESTAGE	GESTAGE	gestational age
LBWGGEST	LBWGGEST	lbw by gestational age
AGEGROUP	AGEGROUP	mom's age group
WTGAINGP	WTGAINGP	mom's weight gain group
LBW_AT_B	LBW_AT_B	mom's weight at her birth
WEIGHT_B	WEIGHT_B	mom's weight before pregnancy
HEIGHT_F	HEIGHT_F	mom's height feet
HEIGHT_I	HEIGHT_I	mom's height inches
FIRST_PR	1st pregn	first pregnancy
YEAR_LAS	YEAR_LAS	year of last pregnancy
MONTH_LA	MONTH_LA	month of last pregnancy
HMO	HMO	pnc covered by hmo?
MEDICAID	MEDICAID	pnc covered by medicaid?
OTHER_IN	OTHER_IN	pnc covered by other health insurance?
NO_COVER	NO_COVER	no pnc coverage
APPOINTM	APPOINTM	mom has problems keeping appointments
MOVED	MOVED	mom moved more than 3 times in last 12 months
UNSAFE	UNSAFE	mom feels unsafe where she lives
HUNGRY	HUNGRY	anyone in household goes to bed hungry?
TOBACCO	TOBACCO	mom used tobacco in last 12 months?
DRUGALCO	DRUGALCO	mom used drug or alcohol in last 12 months?
HURTYOU	HURTYOU	has anyone hit mom or tried to hurt her?
STRESS	STRESS	how do you rate (mom) stress level?
PREFERPG	PREFERPG	if you could change the timing of this pregnancy, would you want it earlier, later, not at all, no change?
POOROUTC	POOROUTC	did last pregnancy result in poor birth outcome? (stillbirth, miscarriage, <5.5 lbs, premature, baby stayed in hospital)
CHRONIC	CHRONIC	mom has chronic illness
CHD_PROV	CHD_PROV	chd provider
DOH_CONT	DOH_CONT	doh provider
PRIVATE	PRIVATE	private provider
TRIMESTE	TRIMESTE	trimester of pregnancy at first visit
OB_HX_FU	OB_HX_FU	number of full term pregnancies
OB_HX_PR	OB_HX_PR	number of pre-term pregnancies
OB_HX_AB	OB_HX_AB	number of abortions
OB_HX_LI	OB_HX_LI	number of live births
OB_HX_LB	OB_HX_LB	number of prior live lbw births
BFD_B	BFD_B	b or fd designation for healthy start screen
V168	V168	certificate number – healthy start
V169	V169	bfd number – healthy start

Appendix A. Continued.

Original Variable Name	New Variable Name	Variable labels
WTKILOGM	WTKILOGM	mom's weight in kilograms
HTMETER	HTMETER	mom's height in meters
BMI	BMI	mom's (bmi) body mass index
RACELABI	RACELABI	infant's race on lab test
ETHLABI	ETHLABI	infant's ethnicity on lab test
CHD_PROG	CHD code	program codes
CTLABINF	CTLABINF	chlamydia test result
GCLABINF	GCLABINF	gonorrhea test result
YLABEXI	YLABEXI	year of lab test
MLABEXI	MLABEXI	month of lab test
DLABEXI	DLABEXI	day of lab test
BFD_C	BFD_C	b or fd designation for infant lab record
V185	V185	certificate number – infant lab
V186	V186	bfd number – infant lab
CITY_B	CITY_B	city for infant morbidity
INFPAT	INFPAT	infant case patient number
INFMORB	INFMORB	infant case morbidity number
DIAGNOSI	DIAGNOSI	infant diagnosis
RPTDATE	RPTDATE	report date 1
RPTDAT1	RPTDAT1	report date 2
RPTDAT2	RPTDAT2	report date 3
DATEEXAM	DATEEXAM	exam date 1
DATEEX1	DATEEX1	exam date 2
DATEEX2	DATEEX2	exam date 3
DATERPT	DATERPT	date reported as a case 1
DATERP1	DATERP1	date reported as a case 2
DATERP2	DATERP2	date reported as a case 3
DATETREA	DATETREA	date of treatment 1
DATETR1	DATETR1	date of treatment 2
DATETR2	DATETR2	date of treatment 3
TREATMEN	TREATMEN	treatment used
BFD_D	BFD_D	b or fd designation for infant case morbidity
V206	V206	certificate number – infant case morbidity
V207	V207	bfd number – infant case morbidity
LABRACEM	LABRACEM	mom's lab race
PROGCODE	PROGCODE	mom program code
CTRESULM	CTRESULM	chlamydia test result
GCRESULM	GCRESULM	gonorrhea test result
YLABCOLM	YLABCOLM	year of lab test
MLABCOLM	MLABCOLM	month of lab test
DLABCOLM	DLABCOLM	day of lab test
BFD_E	BFD_E	b or fd designation for mom lab record
V216	V216	certificate number – mom lab
V217	V217	bfd number – mom lab
MOMPAT	MOMPAT	mom patient number
MOMMORB	MOMMORB	mom morbidity number
V220	V220	mom diagnosis
MOMCASE	MOMCASE	mom case number
YMOMREPT	YMOMREPT	year of report
MMOMREPT	MMOMREPT	month of report
DMOMREPT	DMOMREPT	day of report
YEXMOM	YEXMOM	year of exam
MEXMOM	MEXMOM	month of exam

Appendix A. Continued.

Original Variable Name	New Variable Name	Variable labels
DEXMOM	DEXMOM	day of exam
YTXMOM	YTXMOM	year of treatment
MTXMOM	MTXMOM	month of treatment
DTXMOM	DTXMOM	day of treatment
V231	V231	treatment
BFD_F	BFD_F	b or fd designation for mom case morbidity
V233	V233	certificate number – mom case morbidity
V234	V234	bfd number – mom case morbidity
V235	V235	morbidity file age group

APPENDIX B

SYNTAX

This is the syntax for creation of final logistic variables.

To group the birth weights as LBW, VLBW and outliers.
This leaves birth weights over 2500 as acceptable but codes as missing those under 500 into the missing group. This based on only 304 (.025%) over 2500 in 1996 cohort, this is reasonable, but the 784 (.04%) under 500 is not at 20 weeks gestation.

```
compute BWG=0.
if (BW GE 1500 and BW LE 2499) BWG=1.
if (BW GE 500 and BW LE 1499) BWG=2.
if (BW LE 499) BWG=-1.
missing values BWG (-1).
FORMATS BWG (F8).
VARIABLE LABELS BWG "birth weight group".
VALUE LABELS BWG
 .00000000000000 "NBW >2500"
 1.00000000000000 "LBW  >1500 <2499"
 2.00000000000000 "VLBW  >500 <1499".
```

To calculate gestational age

```
if (LMPD GT 31 or LMPD LT 1) LMPD=15.
compute LMPdays=(LMPY*365.25) + (LMPM*30.4375) + LMPD.
compute CDOBdays=(CDOBY*365.25) + (CDOBM*30.4375) + CDOBD.

compute Gweeks=trunc((CDOBdays-LMPdays)/7).
if (Gweeks GT 42 or Gweeks LT 20) Gweeks=-1.
if (LMPM GT 12 or LMPM LT 1) Gweeks=-1.
if (CDOBM GT 12 or CDOBM LT 1) Gweeks =-1.
missing values Gweeks (-1).

compute gestage=trunc((CDOBdays-LMPdays)/7).
  VARIABLES=gweeks
```

To correct the skewed distribution and treat the "99" values just as other variables for missing values.

```
missing values estgest (-1).
if (estgest eq 99) estgest=-1.
 FREQUENCIES
  VARIABLES= estgest
  /ORDER  ANALYSIS .

FREQUENCIES
  VARIABLES=estgest gweeks allgwks
```

For a trial run on gestational categories matched to birth weight.

```
compute LBWGGest=0.
if (BWG eq 1 and gweeks ge 37) LBWGGest=1.
if (BWG eq 1 and gweeks  le 36) LBWGGest=2.
if (BWG eq 2 and gweeks le 36) LBWGGest=3.
missing values LBWGGest (-1).

FORMATS lbwggest (F8).
VARIABLE LABELS lbwggest "lbw and gest age".
VALUE LABELS lbwggest
 .000000000000000 "TNBW >2500 > 37 weeks"
 1.00000000000000 "TLBW  >1500 <2499 >37 weeks"
 2.00000000000000 "PTLBW >1500 < 2499 <36 weeks"
 3.00000000000000 "PTVLBW  >500 <1499 < 36 weeks".

FREQUENCIES
  VARIABLES=lbwggest
 /HISTOGRAM NORMAL
  /ORDER  ANALYSIS .
```

To create the birth interval indicator variable.

I settled on the nine months from last pregnancy to current birth LMP, since we have paper on analysis to support this in our population, and actually this is closer to the two years of universal standard, since on to the 9 months you add 9 months gestation on to that and reach close to 18 months.

```
compute LLBdays=0.
compute LLBD=15.
compute LLBdays=(LLBY*365.25) + (LLBM*30.4375) + LLBD.
missing values LLBdays (-1).

compute DOTdays=0.
compute DOTD=15.
compute DOTdays=(DOTY*365.25) + (DOTM*30.4375) + DOTD.
missing values DOTdays (-1).
compute lastpreg= LLBdays.
if (DOTdays GT LLBdays) lastpreg = DOTdays.
compute birthint= (LMPdays)-(lastpreg).
missing values birthint (-1).
compute BIindic=0.
if (birthint LT 273.9375) BIindic=1.
missing values BIindic (-1).

VARIABLE LABELS LLBdays "last live birth total days" LLBY "last live birth year"
```

```
 LLBM "last live birth month" LLBD "last live birth day" DOTdays "last other termination
total days"  DOTY "last other termination year"  DOTD "last other termination day"
lastpreg "days since most recent pregnancy" birthint "birth interval in days" BIindic "birth
interval indicator" .
FORMATS BIindic (F8).
VALUE LABELS BIindic
 .000000000000000 "0- birth interval adequate"
 1.00000000000000 "1- birth interval inadequate" .
 FREQUENCIES
  VARIABLES= LLBdays DOTdays lastpreg birthint BIindic
  /ORDER  ANALYSIS .
```

To create a rural indicator variable.

```
compute ruralind=MRCNTY.
recode ruralind (49, 32, 29, 17, 31, 73, 25, 43, 34, 33, 40, 72, 50, 75, 77, 12, 35, 14, 24,
36,
48, 71, 57, 76, 28, 70, 42, 30, 55, 22, 64, 38, 54=1) (else=0).
if (ruralind=0 and MRLIM=2) ruralind=1.
missing values ruralind (-1).
FORMATS ruralind (F8).
VARIABLE LABELS ruralind "rural indicator".
VALUE LABELS ruralind
 .000000000000000 "urban"
 1.00000000000000 "rural" .
```

To create a LBW indicator variable.

```
compute LBWindic=0.
if (BW GE 500 and BW LE 2499) LBWindic=1.
if (BW LE 499) LBWindic=-1.
missing values LBWindic (-1).
FORMATS LBWindic (F8).
VARIABLE LABELS LBWindic "low birth weight indicator".
VALUE LABELS LBWindic
 .000000000000000 "NBW >2500"
 1.00000000000000 "LBW  >500 <2499".
execute.
compute LBWind2=0.
if  (BWG eq 1 and gweeks ge 37)  LBWind2=1.
if (BWG eq 1 and gweeks  le 36) LBWind2=-1.
if (BWG eq 2 and gweeks le 36) LBWind2=-1.
missing values LBWind2 (-1).
FORMATS LBWind2 (F8).
VARIABLE LABELS LBWind2 "term low birth weight indicator".
VALUE LABELS LBWind2
 .000000000000000 "NBW >2500"
```

```
 1.00000000000000 "TLBW  >1500 <2499 >37wks".
execute.
compute LBWind3=0.
if  (BWG eq 1 and gweeks ge 37)  LBWind3=-1.
if (BWG eq 1 and gweeks  le 36) LBWind3=1.
if (BWG eq 2 and gweeks le 36) LBWind3=1.
missing values LBWind3 (-1).
FORMATS LBWind3 (F8).
VARIABLE LABELS LBWind3 "preterm low birth weight indicator".
VALUE LABELS LBWind3
 .000000000000000 "NBW >2500"
 1.00000000000000 "PTLBW  >500 <2499 <36wks".
execute.
```

To create a marital status indicator variable.

```
compute maritali=0.
if (MMS=2) maritali=1.
missing values MMS (-1).
FORMATS maritali (F8).
VARIABLE LABELS maritali "marital status indicator".
VALUE LABELS maritali
 .000000000000000 "married"
 1.00000000000000 "not married".
FREQUENCIES
  VARIABLES=maritali
  /ORDER  ANALYSIS .
```

To create a plural indicator variable to account for plural births.
BUT this only works if you have not first selected out the plural births!

```
compute plurindi=plural.
recode plurindi (2, 3, 4, 5=1) (9=-1) (else=0).
missing values plurindi (-1).
FORMATS plurindi (F8).
VARIABLE LABELS plurindi "plural birth indicator".
VALUE LABELS plurindi
 .000000000000000 "singleton birth"
 1.00000000000000 "plural birth".
```

To create a maternal age indicator variable.

```
compute ageindic=0.
 if (MAGE LT 18 or MAGE GT 40) ageindic=1.
missing values ageindic (-1).
FORMATS ageindic (F8).
VARIABLE LABELS ageindic "maternal age indicator".
```

```
VALUE LABELS ageindic
 .000000000000000 " age between 19 & 40"
 1.00000000000000 "age <18 or >40".

To create a smoker indicator variable birth record.
compute smokindi=0.
 if (TOBUSE =1) smokindi=1.
missing values smokindi (-1).
FORMATS smokindi (F8).
VARIABLE LABELS smokindi "smoker indicator".
VALUE LABELS smokindi
 .000000000000000 " non-smoker"
"smoker".

To create a smoker indicator variable for Healthy Start.
compute smokind2=0.
 if (TOBACCO =1) smokind2=1.
missing values smokind2 (-1).
FORMATS smokind2 (F8).
VARIABLE LABELS smokind2 " HStart smoker indicator".
VALUE LABELS smokind2
 .000000000000000 " non-smoker"
 1.00000000000000 "smoker".

To create a alcohol use indicator variable.
(this is from birth record, use in this pregnancy)
compute alcoindi=0.
 if (alcuse =1) alcoindi=1.
missing values alcoindi (-1).
FORMATS alcoindi (F8).
VARIABLE LABELS alcoindi "alcohol indicator".
VALUE LABELS alcoindi
 .000000000000000 " no alcohol"
 1.00000000000000 "alcohol use".

To create a alcohol use indicator variable.
(this is from Healthy Start file, any time in last 2 months).
compute alcoind2=0.
 if (drugalco =1) alcoind2=1.
missing values alcoind2 (-1).
FORMATS alcoind2 (F8).
VARIABLE LABELS alcoind2 "HS alcohol indicator".
VALUE LABELS alcoind2
 .000000000000000 " no alcohol"
 1.00000000000000 "alcohol use".
```

```
To create a stress indicator variable.
(this combined admission of stress, with violence, hunger, appointment
problems/transportation, multiple moves)
compute stresind=0.
 if (NO_COVER ='1') stresind=1.
 if (APPOINTM=1) stresind=1.
 if (MOVED =1) stresind=1.
 if (UNSAFE =1) stresind=1.
 if (HUNGRY =1) stresind=1.
 if (HURTYOU =1) stresind=1.
 if (STRESS =2) stresind=1.
 if (STRESS =3) stresind=1.
 missing values stresind (-1).
FORMATS stresind (F8).
VARIABLE LABELS stresind "stress full life indicator".
VALUE LABELS stresind
 .000000000000000 "low/no stress"
 1.00000000000000 "high stress".
FREQUENCIES
  VARIABLES=stresind
  /ORDER  ANALYSIS .

To create a mistimed pregnancy  indicator variable.
 (this combined earlier, later, not at all)
compute mistimin=0.
 if (PREFERPG =1) mistimin=1.
 if (PREFERPG=2) mistimin=1.
 if (PREFERPG =3) mistimin=1.
 missing values mistimin (-1).
FORMATS mistimin (F8).
VARIABLE LABELS mistimin "mistimed pregnancy indicator".
VALUE LABELS mistimin
 .000000000000000 "pregnancy timing ok"
 1.00000000000000 "mistimed pregnancy".

To create a prior poor outcome pregnancy  indicator variable.
(this combined prior low birth weight, prior preterm, prior miscarriage, prior stillbirth)
compute poorouti=0.
 if (POOROUTC  eq 1) poorouti=1.
 if (OB_HX_PR ge '1') poorouti=1.
 if (OB_HX_LB ge '1') poorouti=1.
 if  (MHF1 eq 13) poorouti=1.
if (MHF2 eq 13) poorouti=1.
if (MHF3 eq 13)  poorouti=1.
```

```
if  (MHF4 eq 13) poorouti=1.
if (MHF5 eq 13)  poorouti=1.
if (MHF6 eq 13) poorouti=1.
 missing values poorouti (-1).
FORMATS poorouti (F8).
VARIABLE LABELS poorouti "prior poor pregnancy outcome indicator".
VALUE LABELS poorouti
 .000000000000000 "prior pregnancy ok"
 1.00000000000000 "prior poor pregnancy outcome ".
FREQUENCIES
  VARIABLES=poorouti
  /ORDER  ANALYSIS .
```

To create the mom LBW at her birth indicator variable

```
compute momLBW=0.
 if (LBW_AT_B ='Y') momLBW=1.
 if (LBW_AT_B ='N') momLBW=0.
 missing values momLBW (-1).

FORMATS momLBW (F8).
VARIABLE LABELS momLBW "mom was LBW at birth".
VALUE LABELS momLBW
.000000000000000 "mom not LBW at birth"
1.00000000000000 "mom was LBW at birth ".
```

```
To create a medical history indicator variable.
 (this combined chronic health problem, anemia, hypertension, eclampsia, etc from birth
record and Healthy Start)
compute medhind=0.
 if (MHF1 ge '1' and MHF1 le '4') medhind=1.
 if (MHF1 ge '6' and MHF1 le '12') medhind=1.
 if (MHF1 ge '14' and MHF1 le '17') medhind=1.
 if (MHF2 ge '1' and MHF2 le '4') medhind=1.
 if (MHF2 ge '6' and MHF2 le '12') medhind=1.
 if (MHF2 ge '14' and MHF2 le '17') medhind=1.
 if (MHF3 ge '1' and MHF3 le '4') medhind=1.
 if (MHF3 ge '6' and MHF3 le '12') medhind=1.
 if (MHF3 ge '14' and MHF3 le '17') medhind=1.
 if (MHF4 ge 1 and MHF4 le 4) medhind=1.
 if (MHF4 ge 6 and MHF4 le 12) medhind=1.
 if (MHF4 ge 14 and MHF4 le 17) medhind=1.
 if (MHF5 ge 1 and MHF5 le 4) medhind=1.
 if (MHF5 ge 6 and MHF5 le 12) medhind=1.
 if (MHF5 ge 14 and MHF5 le 17) medhind=1.
 if (MHF6 ge 1 and MHF6 le 4) medhind=1.
 if (MHF6 ge 6 and MHF6 le 12) medhind=1.
 if (MHF6 ge 14 and MHF6 le 17) medhind=1.
 if (CHRONIC=1) medhind=1.
 missing values medhind (-1).
execute.
FORMATS medhind (F8).
VARIABLE LABELS medhind "medical history noted in this pregnancy indicator".
VALUE LABELS medhind
 .000000000000000 "no medical history"
 1.00000000000000 "medical history noted in this pregnancy".
FREQUENCIES
 VARIABLES=medhind
 /ORDER  ANALYSIS .
```

```
To create a education indicator variable.
 (this takes into account young age girls still in high school)
compute edindic=0.
 if ((mage ge 18) and (med le 12 or med eq 99)) edindic=1.
 missing values edindic (-1).
FORMATS edindic (F8).
VARIABLE LABELS edindic "education level indicator ".
VALUE LABELS edindic
 .000000000000000 "HS grad or adequate for age"
 1.00000000000000 "less than high school or indicated for age".
FREQUENCIES
  VARIABLES=edindic
  /ORDER  ANALYSIS .

To create a race indicator variable (black only).
compute raceindi=0.
 if (MRACE eq 2) raceindi=1.
 missing values raceindi (-1).
FORMATS raceindi (F8).
VARIABLE LABELS raceindi "black race indicator ".
VALUE LABELS raceindi
 .000000000000000 "mom not black race"
 1.00000000000000 "mom is black race".
FREQUENCIES
  VARIABLES=raceindi
  /ORDER  ANALYSIS .

To create an adequate wt gain indicator.
compute BMIG=0.
if (BMI le 19.79) BMIG=1.
if (BMI ge 19.80 and BMI le 26.00) BMIG=2.
if (BMI ge 26.01 and BMI le 29.00) BMIG=3.
if (BMI ge 29.01) BMIG=4.
missing values BMIG (-1).

FORMATS BMIG (F8).
VARIABLE LABELS BMIG "BMI groups".
VALUE LABELS BMIG
 1.00000000000000 "BMI low < 19.79"
 2.00000000000000 "BMI normal 19.80 to 26.00"
 3.00000000000000 "BMI high 26.01 to 29.00"
 4.00000000000000    "BMI obese > 29.01".
 FREQUENCIES
  VARIABLES= BMIG
 /HISTOGRAM NORMAL
```

```
 /ORDER  ANALYSIS .

To create inadequate weight gain indicator.
compute IAWGindi=0.
if ((BMIG eq 1) and (gweeks ge 37) and ( wtgain LT  28)) IAWGindi=1.
if ((BMIG eq 2) and (gweeks ge 37) and (wtgain LT 25 )) IAWGindi=1.
if ((BMIG eq 3) and (gweeks ge 37) and (wtgain LT 15 )) IAWGindi=1.
if ((BMIG eq 4) and (gweeks ge 37) and (wtgain LT 15 )) IAWGindi=1.
if ((BMIG eq 1) and (gweeks ge 20 and gweeks le 36) and (wtgain LT (12 + (gweeks-
20)))) IAWGindi=1.
if ((BMIG eq 2) and (gweeks ge 20 and gweeks le 36) and (wtgain LT (10.5 + (gweeks-
20)))) IAWGindi=1.
if ((BMIG eq 3) and (gweeks ge 20 and gweeks le 36) and (wtgain LT (7.25 + (gweeks-
20)))) IAWGindi=1.
if ((BMIG eq 4) and (gweeks ge 20 and gweeks le 36) and (wtgain LT (7.25 + (gweeks-
20)))) IAWGindi=1.
missing values IAWGindi (-1).
FORMATS IAWGindi (F8).
VARIABLE LABELS IAWGindi "inadequate weight gain indicator".
VALUE LABELS IAWGindi
 .000000000000000 "adequate weight gain"
 1.00000000000000 "inadequate weight gain"

 FREQUENCIES
  VARIABLES= IAWGindi
  /ORDER  ANALYSIS .

To create a CT and GC infected indicators for mom and infant.
compute CTindic=0.
if (CTRESULM = 1) CTindic=1.
if (CTRESULM = 3 or CTRESULM = 4) CTindic=-1.
missing values CTindic (-1).
FORMATS CTindic (F8).
VARIABLE LABELS CTindic "CT infected mom".
VALUE LABELS CTindic
 .000000000000000 "CT negative"
 1.00000000000000 "CT positive"
compute GCindic=0.
if (GCRESULM = 1) GCindic=1.
if (GCRESULM = 3 or GCRESULM = 4) GCindic=-1.
missing values GCindic (-1).

FORMATS GCindic (F8).
VARIABLE LABELS GCindic "GC infected mom".
VALUE LABELS GCindic
```

```
.000000000000000 "GC negative"
1.00000000000000 "GC positive"

To create an STD now or in pregnancy indicators for mom and infant.
compute STDindi2=0.
if (CTRESULM eq 1) STDindi2=1.
if (GCRESULM eq 1) STDindi2=1.
if (V220 ge 200  and  V220 le 730 ) STDindi2=1.
if (DIAGNOSI le 790) STDindi2=1.
if (CTlabinf eq 1) STDindi2=1.
 if (MHF1 eq '5') STDindi2=1.
 if (MHF2 eq '5') STDindi2=1.
 if (MHF3 eq '5') STDindi2=1.
if (GClabinf eq 1) STDindi2=1.
missing values STDindi2 (-1).
execute.
FORMATS STDindi2 (F8).
VARIABLE LABELS STDindi2 "2 mom or infant with current or past STDs".
VALUE LABELS STDindi2
 .000000000000000 "STD negative mom or infant"
 1.00000000000000 "STD positive mom or infant".

 FREQUENCIES
  VARIABLES= STDindi2
  /ORDER  ANALYSIS .

VARIABLE LABELS bfd_a "birth file" bfd_b "Hstart" bfd_c  "infant lab"
bfd_d "infant morbidity" bfd_e "mom lab" bfd_f "mom morbidity".

To create a PNC indices and indicator.
compute GINDEX=0.
if  (((TRIMESTE eq 1 or TRIMESTE eq 2) and
((GWEEKS ge 22 and GWEEKS le 29) and (PREVIS eq 1)) or
((GWEEKS ge 30 and GWEEKS le 31) and (PREVIS ge 1 and PREVIS le 2)) or
((GWEEKS ge 32 and GWEEKS le 33) and (PREVIS ge 1 and PREVIS le 3)) or
((GWEEKS ge 34 and GWEEKS le 36) and (PREVIS ge 1 and PREVIS le 4)) or
((GWEEKS eq 37) and (PREVIS ge 1) and (PREVIS le 5)) or
((GWEEKS ge 38 and GWEEKS le 39) and (PREVIS ge 1 and PREVIS le 6)) or
((GWEEKS ge  40 and GWEEKS le 41) and (PREVIS ge 1 and PREVIS le 7)) or
((GWEEKS eq 42 and PREVIS ge 1) and (PREVIS le 8)))) GINDEX=1.
if  (((TRIMESTE eq 3) and
((GWEEKS eq 25) and (PREVIS eq 8)) or
((GWEEKS ge 26 and GWEEKS le 31) and (PREVIS ge 1 and PREVIS le 9)) or
((GWEEKS ge 32 and GWEEKS le 35) and (PREVIS ge 1 and PREVIS le 10)) or
((GWEEKS ge 36 and GWEEKS le 37) and (PREVIS ge 1 and PREVIS le 11)) or
```

```
((GWEEKS ge 38 and GWEEKS le 40) and (PREVIS ge 1 and PREVIS le 12)) or
((GWEEKS ge 41 and GWEEKS le 42) and (PREVIS ge 1 and PREVIS le 13))))
GINDEX=1.
if (((PREVIS=0)) or
(TRIMESTE=0) and (PREVIS=99)) GINDEX=1.
if ((PREVIS=99) and (TRIMESTE=0)) or
((TRIMESTE=3) and (GWEEKS ge 1 and GWEEKS le 24)) or
((TRIMESTE=2) and (GWEEKS ge 1 and GWEEKS le 11)) or
((GWEEKS=0) and (PREVIS=0)) or
((TRIMESTE=99) and (PREVIS=0)) or
((TRIMESTE=0) and (PREVIS=0)) GINDEX=1.
missing values GINDEX (-1).
execute.
FORMATS GINDEX (F8).
VARIABLE LABELS GINDEX "PNC indices".
VALUE LABELS GINDEX
 .000000000000000 "adequate access to PNC"
 1.00000000000000 "inadequate access to PNC".

 FREQUENCIES
  VARIABLES= GINDEX
  /ORDER  ANALYSIS .
```

To create a LBWgestational indicator for crosstabs.

```
compute LBWGGind=0.
if (BWG eq 1 and gweeks ge 37) LBWGGind=1.
if (BWG eq 1 and gweeks  le 36) LBWGGind=2.
if (BWG eq 2 and gweeks le 36) LBWGGind=2.
missing values LBWGGest (-1).
FORMATS LBWGGind (F8).
VARIABLE LABELS LBWGGind "lbw group and gest age indicator".
VALUE LABELS LBWGGind
 .000000000000000 "NBW >2500 > 37 weeks"
 1.00000000000000 "TLBW  >1500 <2499 >37 weeks"
 2.00000000000000 "PTLBW >500 < 2499 <36 weeks"
```

To create a method of delivery.

```
compute MODindic=0.
if (MOD1 eq 3 or MOD1 eq 4) MODindic=1.
missing values MODindic (-1).
FORMATS MODindic (F8).
VARIABLE LABELS MODindic "C-section indicator".
VALUE LABELS MODindic
 .000000000000000 "vaginal delivery"
 1.00000000000000 "C-section".
```

To create a variable for all weeks from 1 to 42.
(less the really extreme outliers

```
compute allGwks=trunc((CDOBdays-LMPdays)/7).
if (allGwks GT 42 or allGwks LT 1) allGwks=-1.
if (LMPM GT 12 or LMPM LT 1) allGwks=-1.
if (CDOBM GT 12 or CDOBM LT 1) allGwks =-1.
missing values allGwks (-1).
execute.
FORMATS allGwks (F8).
VARIABLE LABELS allGwks "42 gestational wks".
FREQUENCIES
  VARIABLES=allGwks
  /HISTOGRAM NORMAL
  /ORDER  ANALYSIS .
```

To create a foriegn born indicators for mom and dad.

```
compute momforgn=0.
if (MBST ge 52 and MBST le 59) momforgn=1.
if (MBST ge 88) momforgn=-1.
missing values momforgnT (-1).
execute.
FORMATS momforgn (F8).
VARIABLE LABELS momforgn "mom foreign born".
VALUE LABELS momforgn
 .000000000000000 "US born"
 1.00000000000000 "foreign born".

compute dadforgn=0.
if (FBST ge 52 and FBST le 59) dadforgn=1.
if (FBST ge 88) dadforgn=-1.
missing values dadforgn(-1).
execute.
FORMATS dadforgn (F8).
VARIABLE LABELS dadforgn  "dad foreign born".
VALUE LABELS dadforgn
 .000000000000000 "US born"
 1.00000000000000 "foreign born".
 FREQUENCIES
  VARIABLES= momforgn dadforgn
  /ORDER  ANALYSIS .
```

To create dual infected variable.

```
compute ch=9.
if (ctresulm eq 1) ch=1.
if (ctresulm eq 2) ch=0.
missing values ch (9).
execute.
compute gc=9.
if (gcresulm eq 1) gc=1.
if (gcresulm eq 2) gc=0.
missing values gc (9).
execute.
compute gcch=9.
if (gc eq 0 and ch eq 0) gcch=1.
if (gc eq 1 and ch eq 0) gcch=2.
if (gc eq 0 and ch eq 1) gcch=3.
if (gc eq 1 and ch eq 1) gcch=4.
missing values gcch (9).
execute.
FORMATS gcch (F8).
VARIABLE LABELS gcch  "gcch".
VALUE LABELS gcch 1 'no std'  2 'has gc'  3 'has ct' 4 'has both' .
 FREQUENCIES
 VARIABLES= gcch
 /ORDER  ANALYSIS .
```

To create age groups.

```
RECODE
 age  (1 thru 10=0)  (50 thru Highest=99)  (11 thru 14=1)  (15 thru 19=2)  (20
 thru 24=3)  (25 thru 29=4)  (30 thru 34=5)  (35 thru 39=6)  (40 thru 44=7)
 (45 thru 49=8) INTO agegroup .
VARIABLE LABELS agegroup 'agegroup'.
EXECUTE .
*change decimal point then
VALUE LABELS agegroup
 1  "<14"
 2 "15-19"
 3 "20-24"
 4 "25-29"
 5 "30-34"
 6 "35-39"
 7 "40-44"
 8 "45-49"
 99 "unk".
Execute.
VALUE LABELS V235
```

```
 1  "<14"
 2 "15-19"
 3 "20-24"
 4 "25-29"
 5 "30-34"
 6 "35-39"
 7 "40-44"
 8 "45-49"
 99 "unk".
Execute.
```

To recode race for mom from birth file.

```
compute BMrace=MRACE.
recode BMrace (1=1) (2=2) (else=0).
missing values BMrace (-1).
FORMATS BMrace (F8).
VARIABLE LABELS BMrace "birth mom's race (CHD)".
VALUE LABELS BMrace
.000000000000000 "other"
 1.00000000000000 "white"
2.00000000000000 "black" .
 execute.
```

To recode infant birthrace for CHD sample file.

```
compute BCrace=CRACE.
recode Bcrace (1=1) (2=2) (else=0).
missing values BCrace (-1).
FORMATS BCrace (F8).
VARIABLE LABELS BCrace "birth infant's race (CHD)".
VALUE LABELS BCrace
.000000000000000 "other"
 1.00000000000000 "white"
2.00000000000000 "black" .
 execute.
```

To recode race mom morbidity file.

```
compute BMrace=MRACE.
recode BMrace (1=1) (2=2) (else=0).
missing values BMrace (-1).
FORMATS BMrace (F8).
VARIABLE LABELS BMrace "morbidity mom's race (CHD)".
VALUE LABELS BMrace
.000000000000000 "other"
 1.00000000000000 "white"
2.00000000000000 "black" .
```

```
execute.
FREQUENCIES
 VARIABLES= BMrace
 /ORDER  ANALYSIS .
```

To recode infant birthrace for CHD sample file.

```
compute BCrace=CRACE.
recode Bcrace (1=1) (2=2) (else=0).
missing values BCrace (-1).
FORMATS BCrace (F8).
VARIABLE LABELS BCrace "birth infant's race (CHD)".
VALUE LABELS BCrace
.00000000000000 "other"
 1.00000000000000 "white"
2.00000000000000 "black" .
 execute.
 FREQUENCIES
  VARIABLES= BCrace
  /ORDER  ANALYSIS .
```

To capture HSV for STD now or in past indicators for mom and infant.

```
 compute hsv1=0.
 if (MHF1 eq '05' ) hsv1=1.
missing values hsv1 (-1).
execute.
compute hsv2=0.
 if (MHF2 eq '05' ) hsv2=1.
missing values hsv2 (-1).
execute.
compute hsv3=0.
 if (MHF3 eq '05' ) hsv3=1.
missing values hsv3 (-1).
execute.
FORMATS hsvpg (F8).
VARIABLE LABELS hsvpg "mom or infant with current or past STDs".
VALUE LABELS STDindic
.000000000000000 "no HS identified"
 1.00000000000000 "STD positive mom or infant"
execute.
 FREQUENCIES
  VARIABLES= hsv1 hsv2 hsv3
  /ORDER  ANALYSIS .

compute STDindic=0.
if (CTRESULM eq 1) STDindic=1.
```

```
if (GCRESULM eq 1) STDindic=1.
if (V220 ge 200  and  V220 le 730 ) STDindic=1.
if (DIAGNOSI le 790) STDindic=1.
if (CTlabinf eq 1) STDindic=1.
 if (MHF1 eq ' 5') STDindic=1.
 if (MHF2 eq '05') STDindic=1.
 if (MHF3 eq '05') STDindic=1.
if (GClabinf eq 1) STDindic=1.
missing values STDindic (-1).
execute.
FORMATS STDindic (F8).
VARIABLE LABELS STDindic "mom or infant with current or past STDs".
VALUE LABELS STDindic
 .000000000000000 "STD negative mom or infant"
 1.00000000000000 "STD positive mom or infant"
execute.
 FREQUENCIES
  VARIABLES= STDindic
  /ORDER  ANALYSIS .
```

BIOGRAPHICAL SKETCH

Karla Schmitt is a nursing consultant with the Florida Department of Health, Bureau of STD Prevention and Control. Primary responsibilities include coordination of the Florida Chlamydia and Infertility Prevention Project, Integrated Surveillance Project and Prevalence Studies. Additional responsibilities include development of clinician resources; sexually transmitted infection training courses; and policies, technical guidelines, and protocols applicable to delivery of public health care for sexually transmitted infections. Her previous experience with the Department includes development of family planning policies, implementation of Norplant and Depo-provera programs statewide and the supervision of work directed toward the promotion of building an integrated comprehensive health care system throughout the county health departments. She has also worked as a nurse in home health care, on-call staffing, cancer chemotherapy, and geriatric intermediate care. For many years, Ms. Schmitt worked in Belize, Central America, delivering public health maternal and child health services to indigenous and refugee populations. She is a member of the Florida Nurses Association, Florida Public Health Association, and American Sexually Transmitted Disease Association. She received a Bachelor of Science in Nursing in 1971 from Marquette University in Milwaukee, Wisconsin, a Master of Public Health, international health management in 1993 from the University of South Florida, and Master of Science in Nursing, in 1997 from the University of Florida. She is a women's health nurse practitioner.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Sharleen H. Simpson, Chair
Associate Professor of Nursing

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Donna M. Treloar
Associate Professor of Nursing

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University of South Florida

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the College of Nursing and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy in Nursing.

December, 1999

Dean, College of Nursing

Dean, Graduate School

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